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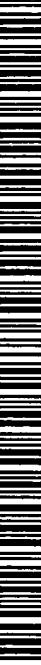
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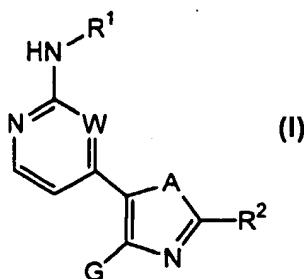
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A1

(54) Title: IMIDAZOLES, OXAZOLES AND THIAZOLES WITH PROTEIN KINASE INHIBITING ACTIVITIES



(57) Abstract: The present invention provides compounds of formula I: (I) or a pharmaceutically acceptable derivative thereof, wherein R¹, R², A, G, and W are as described in the specification. These compounds are inhibitors of protein kinase, particularly inhibitors of JNK, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli, Lck, Src, and Aurora kinases. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

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IMIDAZOLES, OXAZOLES AND THIAZOLES WITH PROTEIN KINASE INHIBITING ACTIVITIESTECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to inhibitors of protein kinase, especially c-Jun N-terminal kinases (JNK) the Src-family of kinases, including Lck, which are members of the mitogen-activated protein (MAP) kinase family, and the Aurora family, including Aurora-2, which are serine/threonine kinases. JNK, Src, Lck, and Aurora-2 have been implicated in a number of different human diseases. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders in which JNK, Src, Lck, and/or Aurora-2 kinases play a role.

BACKGROUND OF THE INVENTION

[0002] Mammalian cells respond to extracellular stimuli by activating signaling cascades that are mediated by members of the mitogen-activated protein (MAP) kinase family, which include the extracellular signal regulated kinases (ERKs), the p38 MAP kinases and the c-Jun N-terminal kinases (JNKs). MAP kinases (MAPKs)

are activated by a variety of signals including growth factors, cytokines, UV radiation, and stress-inducing agents. MAPKs are serine/threonine kinases and their activation occurs by dual phosphorylation of threonine and tyrosine at the Thr-X-Tyr segment in the activation loop. MAPKs phosphorylate various substrates including transcription factors, which in turn regulate the expression of specific sets of genes and thus mediate a specific response to the stimulus.

10 [0003] One particularly interesting kinase family are the c-Jun NH₂-terminal protein kinases, also known as JNKs. Three distinct genes, JNK1, JNK2, JNK3 have been identified and at least ten different splicing isoforms of JNKs exist in mammalian cells [Gupta et al., EMBO J., 15:2760-70 (1996)]. Members of the JNK family are activated by proinflammatory cytokines, such as tumor necrosis factor- α (TNF α) and interleukin-1 β (IL-1 β), as well as by environmental stress, including anisomycin, UV irradiation, hypoxia, and osmotic shock [Minden et al., 20 Biochimica et Biophysica Acta, 1333:F85-F104 (1997)].

[0004] The down-stream substrates of JNKs include transcription factors c-Jun, ATF-2, Elk1, p53 and a cell death domain protein (DENN) [Zhang et al. Proc. Natl. Acad. Sci. USA, 95:2586-91 (1998)]. Each JNK isoform binds to these substrates with different affinities, suggesting a regulation of signaling pathways by substrate specificity of different JNKs *in vivo* [Gupta et al., *supra*].

30 [0005] JNKs, along with other MAPKs, have been implicated in having a role in mediating cellular response to cancer, thrombin-induced platelet aggregation, immunodeficiency disorders, autoimmune diseases, cell death, allergies, osteoporosis and heart

disease. The therapeutic targets related to activation of the JNK pathway include chronic myelogenous leukemia (CML), rheumatoid arthritis, asthma, osteoarthritis, ischemia, cancer and neurodegenerative diseases.

5 [0006] Several reports have detailed the importance of JNK activation associated with liver disease or episodes of hepatic ischemia [Nat. Genet. 21:326-9 (1999); FEBS Lett. 420:201-4 (1997); J. Clin. Invest. 102:1942-50 (1998); and Hepatology 28:1022-30 (1998)]. Therefore, 10 inhibitors of JNK may be useful to treat various hepatic disorders.

15 [0007] A role for JNK in cardiovascular disease such as myocardial infarction or congestive heart failure has also been reported as it has been shown that JNK mediates hypertrophic responses to various forms of cardiac stress [Circ. Res. 83:167-78 (1998); Circulation 97:1731-7 (1998); J. Biol. Chem. 272:28050-6 (1997); Circ. Res. 79:162-73 (1996); Circ. Res. 78:947-53 (1996); and J. Clin. Invest. 97:508-14 (1996)].

20 [0008] It has also been demonstrated that the JNK cascade plays a role in T-cell activation, including activation of the IL-2 promoter. Thus, inhibitors of JNK may have therapeutic value in altering pathologic immune responses [J. Immunol. 162:3176-87 (1999); Eur. J. Immunol. 28:3867-77 (1998); J. Exp. Med. 186:941-53 (1997); and Eur. J. Immunol. 26:989-94 (1996)].

25 [0009] A role for JNK activation in various cancers has also been established, suggesting the potential use of JNK inhibitors in cancer. For example, constitutively activated JNK is associated with HTLV-1 mediated tumorigenesis [Oncogene 13:135-42 (1996)]. JNK may play a role in Kaposi's sarcoma (KS) because it is thought 30 that the proliferative effects of bFGF and OSM on KS

cells are mediated by their activation of the JNK signaling pathway [J. Clin. Invest. 99:1798-804 (1997)]. Other proliferative effects of other cytokines implicated in KS proliferation, such as vascular endothelial growth factor (VEGF), IL-6 and TNF α , may also be mediated by JNK. In addition, regulation of the c-jun gene in p210 BCR-ABL transformed cells corresponds with activity of JNK, suggesting a role for JNK inhibitors in the treatment for chronic myelogenous leukemia (CML) [Blood 92:2450-60 (1998)].

[0010] JNK1 and JNK2 are widely expressed in a variety of tissues. In contrast, JNK3 is selectively expressed in the brain and to a lesser extent in the heart and testis [Gupta et al., *supra*; Mohit et al., Neuron 14:67-78 (1995); and Martin et al., Brain Res. Mol. Brain Res. 35:47-57 (1996)]. JNK3 has been linked to neuronal apoptosis induced by kainic acid, indicating a role of JNK in the pathogenesis of glutamate neurotoxicity. In the adult human brain, JNK3 expression is localized to a subpopulation of pyramidal neurons in the CA1, CA4 and subiculum regions of the hippocampus and layers 3 and 5 of the neocortex [Mohit et al., *supra*]. The CA1 neurons of patients with acute hypoxia showed strong nuclear JNK3-immunoreactivity compared to minimal, diffuse cytoplasmic staining of the hippocampal neurons from brain tissues of normal patients [Zhang et al., *supra*]. Thus, JNK3 appears to be involved in hypoxic and ischemic damage of CA1 neurons in the hippocampus.

[0011] In addition, JNK3 co-localizes immunochemically with neurons vulnerable in Alzheimer's disease [Mohit et al., *supra*]. Disruption of the JNK3 gene caused resistance of mice to the excitotoxic glutamate receptor agonist kainic acid, including the effects on seizure

activity, AP-1 transcriptional activity and apoptosis of hippocampal neurons, indicating that the JNK3 signaling pathway is a critical component in the pathogenesis of glutamate neurotoxicity [Yang et al., Nature, 389:865-870

5 (1997)].

[0012] Based on these findings, JNK signaling, especially that of JNK3, has been implicated in the areas of apoptosis-driven neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, ALS (amyotrophic lateral sclerosis), epilepsy and seizures, Huntington's disease, traumatic brain injuries, as well as ischemic and hemorrhaging stroke.

[0013] The Src-family of kinases are implicated in cancer, immune system dysfunction, and bone remodeling diseases. For general reviews, see Thomas and Brugge, Annu. Rev. Cell Dev. Biol. 13:513 (1997); Lawrence and Niu, Pharmacol. Ther. 77:81 (1998); Tatosyan and Mizenina, Biochemistry (Moscow) 65:49 (2000); and Boschelli et al., Drugs of the Future 2000, 25(7):717

20 (2000).

[0014] Members of the Src family include the following eight kinases in mammals: Src, Fyn, Yes, Fgr, Lyn, Hck, Lck, Blk and Yrc. These are nonreceptor protein kinases that range in molecular mass from 52 to 62 kD. All are characterized by a common structural organization that is comprised of six distinct functional domains: Src homology domain 4 (SH4), a unique domain, SH3 domain, SH2 domain, a catalytic domain (SH1), and a C-terminal regulatory region [Tatosyan et al. Biochemistry (Moscow) 65:49-58 (2000)].

[0015] Based on published studies, Src kinases are considered as potential therapeutic targets for various human diseases. Mice that are deficient in Src develop

osteopetrosis, or bone build-up, because of depressed bone resorption by osteoclasts. This suggests that osteoporosis resulting from abnormally high bone resorption can be treated by inhibiting Src [Soriano et al., Cell, 69:551 (1992) and Soriano et al., Cell, 64: 693 (1991)].

[0016] Suppression of arthritic bone destruction has been achieved by the overexpression of CSK in rheumatoid synoviocytes and osteoclasts [Takayanagi et al., J. Clin. Invest., 104:137 (1999)]. CSK, or C-terminal Src kinase, phosphorylates and thereby inhibits Src catalytic activity. This implies that Src inhibition may prevent joint destruction that is characteristic in patients suffering from rheumatoid arthritis [Boschelli et al., Drugs of the Future 2000, 25(7):717 (2000)].

[0017] Src also plays a role in the replication of hepatitis B virus. The virally encoded transcription factor HBx activates Src in a step required for propagation of the virus [Klein et al., EMBO J., 18:5019, (1999) and Klein et al., Mol. Cell. Biol., 17:6427 (1997)].

[0018] A number of studies have linked Src expression to cancers such as colon, breast, hepatic and pancreatic cancer, certain B-cell leukemias and lymphomas [Talamonti et al., J. Clin. Invest., 91:53 (1993); Lutz et al., Biochem. Biophys. Res. Commun., 243:503 (1998); Rosen et al., J. Biol. Chem., 261:13754 (1986); Bolen et al., Proc. Natl. Acad. Sci. USA, 84:2251 (1987); Masaki et al., Hepatology, 27:1257 (1998); Biscardi et al., Adv. Cancer Res., 76:61 (1999); Lynch et al., Leukemia, 7:1416 (1993)]. Furthermore, antisense Src expressed in ovarian and colon tumor cells has been shown to inhibit tumor

growth [Wiener et al., Clin. Cancer Res., 5:2164 (1999) and Staley et al., Cell Growth Diff., 8:269 (1997)].

[0019] Other Src family kinases are also potential therapeutic targets. Lck plays a role in T-cell signaling. Mice that lack the Lck gene have a poor ability to develop thymocytes. The function of Lck as a positive activator of T-cell signaling suggests that Lck inhibitors may be useful for treating autoimmune disease such as rheumatoid arthritis [Molina et al., Nature, 357: 10 161 (1992)]. Hck, Fgr and Lyn have been identified as important mediators of integrin signaling in myeloid leukocytes [Lowell et al., J. Leukoc. Biol., 65:313 (1999)]. Inhibition of these kinase mediators may therefore be useful for treating inflammation [Boschelli et al., Drugs of the Future 2000, 25(7):717 (2000)].

[0020] The Aurora family of serine/threonine kinases is essential for cell proliferation [Bischoff, J.R. & Plowman, G.D. Trends in Cell Biology et al., 9:454-459 (1999); Giet et al. Journal of Cell Science, 112:3591-20 3601 (1999); Nigg Nat. Rev. Mol. Cell Biol. 2:21-32 (2001); Adams et al., Trends in Cell Biology 11:49-54 (2001)]. Inhibitors of the Aurora kinase family therefore have the potential to block growth of all tumour types.

[0021] The three known mammalian family members, Aurora-A ("1"), B ("2") and C ("3"), are highly homologous proteins responsible for chromosome segregation, mitotic spindle function and cytokinesis. Aurora expression is low or undetectable in resting cells, with expression and activity peaking during the G2 and mitotic phases in cycling cells. In mammalian cells proposed substrates for Aurora include histone H3, a protein involved in chromosome condensation, and CENP-A,

myosin II regulatory light chain, protein phosphatase 1, [0022] Since its discovery in 1997 the mammalian Aurora kinase family has been closely linked to tumorigenesis. The most compelling evidence for this is 5 that over-expression of Aurora-A transforms rodent fibroblasts [Bischoff et al., EMBO J., 17:3052-3065 (1998)]. Cells with elevated levels of this kinase contain multiple centrosomes and multipolar spindles, and rapidly become aneuploid. The oncogenic activity of 10 Aurora kinases is likely to be linked to the generation of such genetic instability. Indeed, a correlation between amplification of the aurora-A locus and chromosomal instability in mammary and gastric tumours has been observed. [Miyoshi et al.. Int. J. Cancer, 15 92:370-373 (2001) and Sakakura et al. British Journal of Cancer, 84:824-831 (2001)]. The Aurora kinases have been reported to be over-expressed in a wide range of human tumours. Elevated expression of Aurora-A has been detected in over 50% of colorectal [Bischoff et al., EMBO J., 20 17:3052-3065 (1998) and Takahashi et al., Jpn. J. Cancer Res., 91:1007-1014 (2000)] ovarian [Gritsko et al. Clinical Cancer Research, 9:1420-1426 (2003)], and gastric tumors [Sakakura et al., British Journal of Cancer, 84:824-831 (2001)], and in 94% of invasive duct 25 adenocarcinomas of the breast [Tanaka et al. Cancer Research, 59:2041-2044 (1999)]. High levels of Aurora-A have also been reported in renal, cervical, neuroblastoma, melanoma, lymphoma, pancreatic and prostate tumour cell lines. [Bischoff et al., EMBO J., 30 17:3052-3065 (1998); Kimura et al. J. Biol. Chem., 274:7334-7340 (1999); Zhou et al., Nature Genetics, 20:189-193 (1998); Li et al., Clin Cancer Res. 9(3):991-7 (2003)]. Amplification/overexpression of Aurora-A is

- 9 -

- observed in human bladder cancers and amplification of Aurora-A is associated with aneuploidy and aggressive clinical behaviour [Sen et al., J Natl Cancer Inst., 94(17):1320-9 (2002)]. Moreover, amplification of the aurora-A locus (20q13) correlates with poor prognosis for patients with node-negative breast cancer [Isola, American Journal of Pathology 147, 905-911 (1995)].
- Aurora-B is highly expressed in multiple human tumour cell lines, including leukemic cells [Katayama et al., Gene 244:1-7)]. Levels of this enzyme increase as a function of Duke's stage in primary colorectal cancers [Katayama et al., J. Natl Cancer Inst., 91:1160-1162 (1999)]. Aurora-C, which is normally only found in germ cells, is also over-expressed in a high percentage of primary colorectal cancers and in a variety of tumour cell lines including cervical adenocarcinoma and breast carcinoma cells [Kimura et al., J. Biol. Chem. 274:7334-7340 (1999) and Takahashi et al., Jpn. J. Cancer Res., 91:1007-1014 (2000)].
- [0008] Based on the known function of the Aurora kinases, inhibition of their activity should disrupt mitosis leading to cell cycle arrest. In vivo, an Aurora inhibitor therefore slows tumor growth and induces regression.
- [0023] Elevated levels of all Aurora family members are observed in a wide variety of tumour cell lines. Aurora kinases are over-expressed in many human tumors and this is reported to be associated with chromosomal instability in mammary tumors.
- [0024] Aurora-2 is highly expressed in multiple human tumor cell lines and levels increase as a function of Duke's stage in primary colorectal cancers [Katayama et al., J. Natl Cancer Inst., 91:1160-1162 (1999)]. Aurora-

- 10 -

2 plays a role in controlling the accurate segregation of chromosomes during mitosis. Misregulation of the cell cycle can lead to cellular proliferation and other abnormalities. In human colon cancer tissue, the Aurora-2 protein has been found to be over expressed [Bischoff et al., EMBO J., 17: 3052-3065 (1998); Schumacher et al., J. Cell Biol., 143:1635-1646 (1998); Kimura et al., J. Biol. Chem., 272: 13766-13771 (1997)]. Aurora-2 is over-expressed in the majority of transformed cells. Bischoff et al found high levels of Aurora-2 in 96% of cell lines derived from lung, colon, renal, melanoma and breast tumors [Bischoff et al., EMBO J., 17:3052-3065 (1998)]. Two extensive studies show elevated Aurora-2 in 54% and 68% [Bishoff et al., EMBO J., 17:3052-3065 and Takahashi et al. Jpn J Cancer Res. 91:1007-1014 (2000)] of colorectal tumours and in 94% of invasive duct adenocarcinomas of the breast (Tanaka et al., Cancer Research, 59:2041-2044 (1999)].

[0025] Aurora-1 expression is elevated in cell lines derived from tumors of the colon, breast, lung, melanoma, kidney, ovary, pancreas, CNS, gastric tract and leukemias (Tatsuka et al 1998 58, 4811-4816).

[0026] High levels of Aurora-3 have been detected in several tumour cell lines, although it is restricted to testis in normal tissues [Kimura et al. Journal of Biological Chemistry, 274:7334-7340 (1999)]. Over-expression of Aurora-3 in a high percentage (c. 50%) of colorectal cancers has also been documented (Takahashi et al., Jpn J. Cancer Res. 91:1007-1014 (2001)]. In contrast, the Aurora family is expressed at a low level in the majority of normal tissues, the exceptions being tissues with a high proportion of dividing cells such as

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the thymus and testis [Bischoff et al EMBO J., 17:3052-3065 (1998)].

[0027] For further review of the role Aurora kinases play in proliferative disorders, see Bischoff et al.,

5 Trends in Cell Biology 9:454-459 (1999); Giet et al.

Journal of Cell Science, 112:3591-3601 (1999); Nigg et

al., Nat. Rev. Mol. Cell Biol., 2:21-32 (2001) et al.,

Trends in Cell Biology, 11:49-54 (2001); and Dutertre,

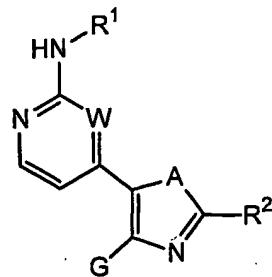
et al. Oncogene, 21:6175-6183 (2002).

10 [0028] There is a continued need to develop potent inhibitors of JNKs, Src family kinases, and Aurora family kinases that are useful in treating or preventing various conditions associated with JNK, Src, and Aurora activation.

15

SUMMARY OF THE INVENTION

[0029] The present invention provides compounds of formula I:



I

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or a pharmaceutically acceptable derivative thereof, wherein R¹, R², A, G, and W are as described below.

[0030] The present invention also provides a pharmaceutical composition comprising a compound of formula I.

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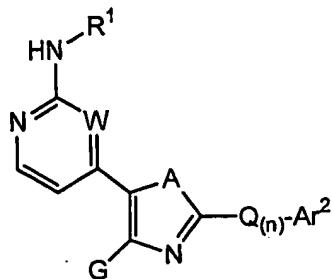
[0031] The compounds and pharmaceutical compositions of the present invention are useful as inhibitors of c-Jun N-terminal kinases (JNK) Src family kinases,

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including Src and Lck, and Aurora family kinases, including Aurora-2. Thus, they are also useful in methods for treating or preventing a variety of disorders, such as heart disease, immunodeficiency 5 disorders, inflammatory diseases, allergic diseases, autoimmune diseases, destructive bone disorders such as osteoporosis, proliferative disorders, infectious diseases and viral diseases. The compositions are also useful in methods for preventing cell death and 10 hyperplasia and therefore may be used to treat or prevent reperfusion/ischemia in stroke, heart attacks, and organ hypoxia. The compositions are also useful in methods for preventing thrombin-induced platelet aggregation. The compositions are especially useful for disorders such as 15 chronic myelogenous leukemia (CML), rheumatoid arthritis, asthma, osteoarthritis, ischemia, cancer, liver disease including hepatic ischemia, heart disease such as myocardial infarction and congestive heart failure, pathologic immune conditions involving T cell activation 20 and neurodegenerative disorders.

DETAILED DESCRIPTION OF THE INVENTION

[0032] The present invention provides a compound of formula I:



25

I

or a pharmaceutically acceptable derivative thereof, wherein:

W is nitrogen or CH;

G is hydrogen or C₁₋₃ aliphatic wherein one methylene unit of G is optionally replaced by -C(O)-, -C(O)O-, -C(O)NH-, -SO₂-, or -SO₂NH-;

5 A is -N-T_(n)-R, oxygen, or sulfur;

R¹ is selected from -T_(n)-R or -T_(n)-Ar¹;

each n is independently 0 or 1;

T is a C₁₋₄ alkylidene chain wherein one methylene unit of T is optionally replaced by -C(O)-, -C(O)O-, -C(O)NH-,

10 -SO₂-, or -SO₂NH-;

Ar¹ is a 3-7 membered monocyclic saturated, partially saturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 8-10 membered bicyclic saturated,

15 partially saturated, or aromatic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each member of Ar¹ is optionally substituted with one -Z-R³ and one to three additional groups independently selected from -R,

20 halogen, oxo, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -OC(O)R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -NRSO₂R, -NRSO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R;

each R is independently selected from hydrogen or a C₁₋₆

25 aliphatic, wherein said aliphatic is optionally substituted with one to three groups independently selected from oxo, -CO₂R', -OR', -N(R')₂, -SR', -NO₂, -NR'C(O)R', -NR'C(O)N(R')₂, -NR'CO₂R', -C(O)R', -OC(O)R', -C(O)N(R')₂, -OC(O)N(R')₂, -S(O)R', -SO₂R',

30 -SO₂N(R')₂, -NR'SO₂R', -NR'SO₂N(R')₂, -C(O)C(O)R', -C(O)CH₂C(O)R', halogen, or -CN, or two R bound to the same nitrogen atom are taken together with that nitrogen atom to form a five or six membered

heterocyclic or heteroaryl ring having one to two additional heteroatoms independently selected from oxygen, nitrogen, or sulfur;

each R' is independently selected from hydrogen or C₁₋₆

5 aliphatic, wherein said aliphatic is optionally substituted with one to three groups independently selected from oxo, -CO₂H, -OH, -NH₂, -SH, -NO₂, -NHC(O)H, -NHC(O)NH₂, -NHCO₂H, -C(O)H, -OC(O)H, -C(O)NH₂, -OC(O)NH₂, -S(O)H, -SO₂H, -SO₂NH₂, -NSO₂H,

10 -NSO₂NH₂, -C(O)C(O)H, -C(O)CH₂C(O)H, halogen, or -CN, or two R' bound to the same nitrogen atom are taken together with that nitrogen atom to form a five or six membered heterocyclic or heteroaryl ring optionally having one or two additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

15 Z is a C_{1-C₆} alkylidene chain wherein up to two non-adjacent methylene units of Z are optionally replaced by -C(O)-, -C(O)O-, -C(O)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)N(R)-, -N(R)N(R)C(O)-, -N(R)C(O)-,

20 -N(R)C(O)O-, -N(R)C(O)N(R)-, -S(O)-, -SO₂-, -N(R)SO₂-,-SO₂N(R)-, -N(R)SO₂N(R)-, -O-, -S-, or -N(R)-;

R² is -Q_(n)-Ar²;

Ar² is selected from a 3-7 membered monocyclic saturated, partially saturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 8-10 membered bicyclic saturated, partially saturated, or aromatic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each member of Ar² is

25 optionally substituted with 1-5 groups independently selected from -Z-R³, -R, halogen, oxo, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R,

30

- 15 -

$-\text{CO}_2\text{R}$, $-\text{OC(O)R}$, $-\text{C(O)N(R)}_2$, $-\text{OC(O)N(R)}_2$, $-\text{S(O)R}$, $-\text{SO}_2\text{R}$,
 $-\text{SO}_2\text{N(R)}_2$, $-\text{N(R)SO}_2\text{R}$, $-\text{N(R)SO}_2\text{N(R)}_2$, $-\text{C(O)C(O)R}$, or
 $-\text{C(O)CH}_2\text{C(O)R}$;

- Q is a C_{1-3} alkylidene chain wherein up to two non-
5 adjacent methylene units of Q are optionally replaced by $-\text{C(O)-}$, $-\text{C(O)O-}$, $-\text{C(O)C(O)-}$, $-\text{C(O)N(R)-}$,
 $-\text{OC(O)N(R)-}$, $-\text{N(R)N(R)-}$, $-\text{N(R)N(R)C(O)-}$, $-\text{N(R)C(O)-}$,
 $-\text{N(R)C(O)O-}$, $-\text{N(R)C(O)N(R)-}$, $-\text{S(O)-}$, $-\text{SO}_2-$, $-\text{N(R)SO}_2-$,
 $-\text{SO}_2\text{N(R)-}$, $-\text{N(R)SO}_2\text{N(R)-}$, $-\text{O-}$, $-\text{S-}$, or $-\text{N(R)-}$;
10 R^3 is selected from $-\text{Ar}^3$, $-\text{R}$, halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}$,
 $-\text{SR}$, $-\text{N(R)}_2$, $-\text{NRC(O)R}$, $-\text{NRC(O)N(R)}_2$, $-\text{NRCO}_2\text{R}$, $-\text{C(O)R}$,
 $-\text{CO}_2\text{R}$, $-\text{OC(O)R}$, $-\text{C(O)N(R)}_2$, $-\text{OC(O)N(R)}_2$, $-\text{SOR}$, $-\text{SO}_2\text{R}$,
 $-\text{SO}_2\text{N(R)}_2$, $-\text{NRSO}_2\text{R}$, $-\text{NRSO}_2\text{N(R)}_2$, $-\text{C(O)C(O)R}$, or
 $-\text{C(O)CH}_2\text{C(O)R}$; and

- 15 Ar^3 is a 5-6 membered saturated, partially saturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each member of Ar^3 is optionally substituted with halogen, oxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{R}'$, $-\text{OR}'$, $-\text{N(R')}_2$, $-\text{N(R')}C(O)\text{R}'$, $-\text{N(R')}C(O)\text{N(R')}_2$, $-\text{N(R')}CO_2\text{R}'$, $-\text{C(O)R}'$, $-\text{CO}_2\text{R}'$, $-\text{OC(O)R}'$, $-\text{C(O)N(R')}_2$, $-\text{OC(O)N(R')}_2$, or $-\text{SO}_2\text{R}'$;
20 provided that when W is nitrogen and:

- (i) A is $-\text{N-T}_{(n)}-\text{R}$ and R^2 is a saturated ring or
 - (ii) A is sulfur,
- 25 then R^1 is other than an optionally substituted phenyl.

[0033] The following abbreviations are used throughout the specifications (including in chemical formulae):

iPr = isopropyl

30 t-Bu or tBu = tert-butyl

Et = ethyl

Me = methyl

Cbz = benzyloxycarbonyl

BOC = *tert*-butyloxycarbonyl

Ph = phenyl

Bn = benzyl

DMF = N,N-dimethylformamide THF = tetrahydrofuran

5 DCM = dichloromethane

MOM = methoxymethyl

DMSO = dimethylsulfoxide

TLC = thin layer chromatography

[0034] As used herein, the following definitions shall
10 apply unless otherwise indicated.

[0035] The phrase "optionally substituted" is used
interchangeably with the phrase "substituted or
unsubstituted". Unless otherwise indicated, an
optionally substituted group may have a substituent at
15 each substitutable position of the group, and each
substitution is independent of each other.

[0036] The term "aliphatic" or "aliphatic group" as
used herein means a straight-chain or branched C₁-C₁₂
hydrocarbon chain that is completely saturated or that
20 contains one or more units of unsaturation, or a
monocyclic C₃-C₈ hydrocarbon or bicyclic C₈-C₁₂ hydrocarbon
ring system that is completely saturated or that contains
one or more units of unsaturation, but which is not
aromatic (also referred to herein as "carbocycle",
25 "carbocyclic", "carbocyclo", or "cycloalkyl"), that has a
single point of attachment to the rest of the molecule
wherein any individual ring in said bicyclic ring system
has 3-7 members. For example, suitable aliphatic groups
include, but are not limited to, linear or branched
30 alkyl, alkenyl or alkynyl groups and hybrids thereof such
as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or
(cycloalkyl)alkenyl.

- [0037] The terms "alkyl", "hydroxyalkyl" and "alkoxyalkyl", used alone or as part of a larger moiety, unless otherwise indicated, include both straight and branched saturated hydrocarbon chains containing one to 5 twelve carbon atoms. The term "alkenyl" used alone or as part of a larger moiety shall include both straight and branched hydrocarbon chains containing two to twelve carbon atoms and having at least one carbon-carbon double bond. The term "alkynyl" used alone or as part of a 10 larger moiety shall include both straight and branched hydrocarbon chains containing two to twelve carbon atoms and having at least one carbon-carbon triple bond. The term "alkoxy" used alone or as part of a larger moiety refers to an -O-alkyl, -O-alkenyl, or -O-alkynyl radical.
- 15 [0038] The term "carbocycle", "carbocyclyl", "carbocyclo" or "carbocyclic" also includes hydrocarbon rings that are fused to one or more aromatic or nonaromatic rings, such as in a decahydronaphthyl or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring.
- 20 [0039] The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" mean alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.
- 25 [0040] The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen. As an example, in a saturated or partially 30 saturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl).

[0041] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring systems having a total of five to fourteen ring members, such as phenyl, benzyl, phenethyl, 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to rings that are optionally substituted. "Aryl" also includes fused polycyclic aromatic ring systems in which an aromatic ring is fused to one or more rings. Examples include 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as in an indanyl, phenanthridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

[0042] The term "aralkyl" refers to an alkyl, alkenyl or alkynyl group substituted by an aryl. Examples of aralkyl groups include, but are not limited to, benzyl and phenethyl. The term "aralkoxy" refers to an alkoxy group substituted by an aryl. The term "aryloxyalkyl" refers to an alkyl, alkenyl or alkynyl group substituted by an -O-aryl.

[0043] The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein includes non-aromatic monocyclic, bicyclic or tricyclic ring systems having five to fourteen ring members, preferably five to ten, in which one or more ring members is a heteroatom, wherein each ring in the system contains 3 to 7 ring members.

[0044] Examples of heterocyclic rings include 3-1H-benzimidazol-2-one, (1-substituted)-2-oxo-benzimidazol-3-yl, 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 5 4-tetrahydropyranyl, [1,3]-dioxalanyl, [1,3]-dithiolanyl, [1,3]-dioxanyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 10 3-pyrrolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-phthalimidinyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, 15 benzothiolanyl, and benzothianyl. Also included within the scope of the term "heterocyclyl" or "heterocyclic", as it is used herein, is a group in which a non-aromatic heteroatom-containing ring is fused to one or more aromatic or non-aromatic rings, such as in an indolinyl, 20 chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the non-aromatic heteroatom-containing ring. The term "heterocycle", "heterocyclyl", or "heterocyclic" whether saturated or partially saturated, also refers to rings 25 that are optionally substituted. The term "heterocyclalkyl" refers to an alkyl, alkenyl or alkynyl group substituted by a heterocyclyl.

[0045] The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or 30 "heteroarylalkoxy", refers to monocyclic, bicyclic or tricyclic heteroaromatic ring systems having five to fourteen members, preferably five to ten, wherein each ring in the system contains 3 to 7 ring members in which

one or more ring carbons, preferably one to four, are each replaced by a heteroatom. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic". The term "heteroaryl" also 5 refers to rings that are optionally substituted.

[0046] Examples of heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 10 5-oxazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 5-tetrazolyl, 2-triazolyl, 5-triazolyl, 15 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, indazolyl, isoindolyl, acridinyl, and benzoisoxazolyl.

[0047] Also included within the scope of the term "heteroaryl", as it is used herein, is a group in which a heteroatomic ring is fused to one or more aromatic or nonaromatic rings where the radical or point of attachment is on the heteroaromatic ring. Examples 20 include tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[3,4-d]pyrimidinyl. The term "heteroaralkyl" refers to an alkyl, alkenyl or alkynyl group substituted by a heteroaryl. The term "heteroarylalkoxy" refers to an alkoxy group substituted by a heteroaryl.

[0048] An aryl (including the aryl moiety in aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including the heteroaryl moiety in heteroaralkyl and heteroarylalkoxy and the like) group may contain one or 30

more substituents. Determination of a suitable number of substituents on any given moiety is within the understanding of the skilled artisan. Suitable substituents on the unsaturated carbon atom of an aryl, heteroaryl, aralkyl, or heteroaralkyl group are selected from halogen, $-R^\circ$, $-OR^\circ$, $-SR^\circ$, 1,2-methylenedioxy, 1,2-ethylenedioxy, phenyl (Ph) optionally substituted with R° , $-O(Ph)$ optionally substituted with R° , $-CH_2(Ph)$ optionally substituted with R° , $-CH_2CH_2(Ph)$ optionally substituted with R° , $-NO_2$, $-CN$, $-N(R^\circ)_2$, $-NR^\circ C(O)R^\circ$, $-NR^\circ C(O)N(R^\circ)_2$, $-NR^\circ CO_2R^\circ$, $-NR^\circ NR^\circ C(O)R^\circ$, $-NR^\circ NR^\circ C(O)N(R^\circ)_2$, $-NR^\circ NR^\circ CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-OC(O)R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R^\circ)_2$, $-S(O)R^\circ$, $-NR^\circ SO_2N(R^\circ)_2$, $-NR^\circ SO_2R^\circ$, $-C(=S)N(R^\circ)_2$, $-C(=NH)-N(R^\circ)_2$, or $-(CH_2)_yNHC(O)R^\circ$, wherein y is 1-4 and each R° is independently selected from hydrogen, optionally substituted C₁₋₆ aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, $-O(Ph)$, or $-CH_2(Ph)$. Optional substituents on the aliphatic group of R° are selected from $-NH_2$, $-NH(C_{1-4}$ unsubstituted aliphatic), $-N(C_{1-4}$ unsubstituted aliphatic)₂, halogen, $-C_{1-4}$ unsubstituted aliphatic, $-OH$, $-O(C_{1-4}$ unsubstituted aliphatic), $-NO_2$, $-CN$, $-CO_2H$, $-CO_2(C_{1-4}$ unsubstituted aliphatic), $-O(halo C_{1-4}$ unsubstituted aliphatic), or halo C₁₋₄ unsubstituted aliphatic.

[0049] An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and the following:

=O, =S, =NNHR*, =NN(R*)₂, =NNHC(O)R*, =NNHCO₂(alkyl), =NNHSO₂(alkyl), or =NR*, where each R* is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic. Optional substituents on the aliphatic group 5 of R* are selected from -NH₂, -NH(C₁₋₄ unsubstituted aliphatic), -N(C₁₋₄ unsubstituted aliphatic)₂, halogen, C₁₋₄ unsubstituted aliphatic, -OH, -O(C₁₋₄ unsubstituted aliphatic), -NO₂, -CN, -CO₂H, -CO₂(C₁₋₄ unsubstituted aliphatic), -O(halo C₁₋₄ unsubstituted aliphatic), or 10 halo(C₁₋₄ unsubstituted aliphatic).

[0050] Optional substituents on the nitrogen of a non-aromatic heterocyclic ring are selected from -R*, -N(R*)₂, -C(O)R*, -CO₂R*, -C(O)C(O)R*, -C(O)CH₂C(O)R*, -SO₂R*, -SO₂N(R*)₂, -C(=S)N(R*)₂, -C(=NH)-N(R*)₂, or -NR⁺SO₂R*; 15 wherein R* is hydrogen, an optionally substituted C₁₋₆ aliphatic, optionally substituted phenyl, optionally substituted -O(Ph), optionally substituted -CH₂(Ph), optionally substituted -CH₂CH₂(Ph), or an unsubstituted 5-6 membered heteroaryl or heterocyclic ring. Optional 20 substituents on the aliphatic group or the phenyl ring of R* are selected from -NH₂, -NH(C₁₋₄ unsubstituted aliphatic), N(C₁₋₄ unsubstituted aliphatic)₂, halogen, C₁₋₄ unsubstituted aliphatic, -OH, -O(C₁₋₄ unsubstituted aliphatic), -NO₂, -CN, -CO₂H, -CO₂(C₁₋₄ unsubstituted aliphatic), -O(halo C₁₋₄ unsubstituted aliphatic), or 25 halo(C₁₋₄ unsubstituted aliphatic).

[0051] The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one or more units of unsaturation.

30 [0052] A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one that is

not substantially altered when kept at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

[0053] It will be apparent to one skilled in the art 5 that certain compounds of this invention may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the invention.

[0054] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms 10 of the structure; i.e., the R and S configurations for each asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, structures 15 depicted herein are also meant to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of 20 a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

[0055] Preferred R¹ groups of formula I are selected 25 from hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene chain and Ar¹ is an optionally substituted 6-membered saturated, partially saturated, or aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur. More preferred R¹ groups of formula I are selected from phenyl, benzyl, pyridyl, piperidinyl, or cyclohexyl. Preferred substituents on R¹ are selected 30 from -CO₂R, -OR, -Z-R³, halogen, -NRSO₂R, -SO₂N(R)₂, -NRCON(R)₂, -NO₂, or -N(R)₂. More preferred substituents of R¹ are selected from benzyloxy, phenoxy, -SO₂NH₂, -OH, -NO₂, -NH₂, -OMe, -Br, -Cl, -CO₂Me, -NHSO₂Me, -NHSO₂Et,

-NHCON(Me)₂, -NHCON(Et)₂, -NHCOPyrrolidin-1-yl, or
-NHCOMorpholin-4-yl.

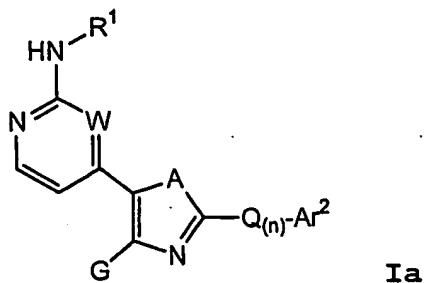
[0056] Most preferred R¹ groups of formula I are those wherein R¹ is -CH₂-Ar¹ or Ar¹. Preferred -Z-R³ groups of the Ar¹ group of formula I are those wherein Z is a C₁₋₄ alkylidene chain wherein one methylene unit of Z is optionally replaced by -O-, -NH-, -NHC(O)-, -NHC(O)O-, -NHSO₂-, -C(O)NH-, and wherein R³ is selected from -N(R)₂, -NHC(O)R, or Ar³ wherein Ar³ is a 5-6 membered heterocyclic or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen, or sulfur. The Ar³ group is optionally substituted with -R', -OR', -N(R')₂, or oxo. More preferred Z-R³ groups of the Ar¹ group of formula I are selected from -O-CH₂-phenyl, -O(CH₂)₃OH, -O(CH₂)₃NH(CH₂)₂OH, -O(CH₂)₂NH(CH₂)₂OH, -O(CH₂)₃N(hydroxyethyl)(methyl), -O(CH₂)₃pyrrolidin-1-yl, -O(CH₂)₂morpholin-4-yl, -O(CH₂)₃N(Me)₂, -O(CH₂)₃N(Et)₂, -O(CH₂)₃(4-hydroxyethyl piperazin-1-yl), -O(CH₂)₃piperazin-1-yl, -O(CH₂)₃(4-hydroxymethylpiperidin-1-yl), -O(CH₂)₃(4-hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂, -NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-aminothiazol-4-yl), -NHCOCH₂cyclopropyl, -NHCO(CH₂)₂N(Et)₂, -NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHC(O)-pyrrolidin-1-yl, -NHCOMorpholin-4-yl, -NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl, -NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl.

[0057] Preferred R² groups of formula I are selected from Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclic or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen

or sulfur, wherein Ar² is optionally substituted with one to five groups independently selected from -Z-R³, -R, halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂, 5 -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R. More preferred R² groups of formula I are selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl. Preferred Z is a C₁₋₄ alkylidene chain and 10 wherein one methylene unit of Z is optionally replaced by -S-, -O-, -N(R)-, or -C(O)O-. Preferred substituents on Ar² are selected from -Z-Ar³, -R, halogen, -OR, -N(R)₂, or -CO₂R, wherein Ar³ is an optionally substituted 5-6 membered aryl ring having zero to two heteroatoms 15 independently selected from nitrogen, oxygen, or sulfur. More preferred substituents on Ar² are selected from phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 20 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, halogen such as chloro, bromo, and fluoro, haloalkyl such as trifluoromethyl, -OH, -NH₂, alkyl such as methyl, or alkoxy such as methoxy and ethoxy. 25 [0058] Preferred G is hydrogen, C₁₋₃ aliphatic, or C_{1-C₃} aliphatic wherein one methylene unit of G is replaced by -C(O)-. More preferred G is hydrogen.

[0059] Preferred A is -NH, -N-CH₃, -N-CH₂-OCH₃, oxygen, or sulfur.

30 [0060] One embodiment of this invention relates to compounds of formula Ia:

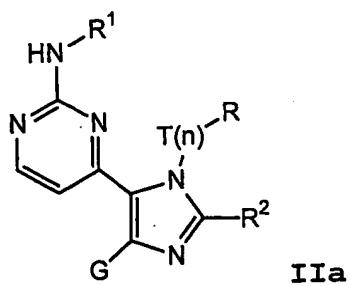


Ia

or a pharmaceutically acceptable derivative thereof,
wherein R¹, R, T, W, A, Q, Ar² and G are as described
above. Preferred R¹, Ar², A, and G are as described above
5 for formula I.

[0061] Preferred Q is a C₁-C₃ alkylidene chain; or a
C₁-C₃ alkylidene chain with one methylene unit replaced by
-O-.

[0062] Another embodiment of this invention relates to
10 compounds of formula IIa:



IIa

or a pharmaceutically acceptable derivative thereof,
wherein R¹, R², R, T, and G are as described above.
[0063] Preferred R¹ groups of formula IIa are selected
15 from hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene
chain wherein one -CH₂- unit of T is optionally replaced
by -C(O)-, -C(O)O-, -C(O)NH-, -SO₂- or -SO₂NH-,
and Ar¹ is an optionally substituted 6-membered saturated,
partially saturated, or aryl ring having zero to two
20 heteroatoms independently selected from nitrogen, oxygen,
or sulfur. More preferred R¹ groups of formula IIa are
selected from phenyl, benzyl, pyridyl, piperidinyl, or

cyclohexyl. Preferred substituents on R¹ are selected from -CO₂R, -OR, -Z-R³, halogen, -NRSO₂R, -SO₂N(R)₂, -NRCON(R)₂, -NO₂, or -N(R)₂. More preferred substituents of R¹ are selected from benzyloxy, phenoxy, -SO₂NH₂, -OH, -NO₂, -NH₂, -OMe, -Br, -Cl, -CO₂Me, -NHSO₂Me, -NHSO₂Et, -NHCON(Me)₂, -NHCON(Et)₂, -NHCOpyrrolidin-1-yl, or -NHCOMorpholin-4-yl.

[0064] Preferred R² groups of formula IIa are selected from Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein Ar² is optionally substituted with one to five groups independently selected from -Z-R³, -R, halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R. More preferred R² groups of formula IIa are selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl. Preferred Z is a C₁₋₄ alkylidene chain and wherein one methylene unit of Z is optionally replaced by -S-, -O-, -N(R)-, or -C(O)O-. Preferred substituents on Ar² are selected from -Z-Ar³, -R, halogen, -OR, -N(R)₂, or -CO₂R, wherein Ar³ is an optionally substituted 5-6 membered aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur. More preferred substituents on Ar² are selected from phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl,

pyrimidinyl, halogen such as chloro, bromo, and fluoro, haloalkyl such as trifluoromethyl, -OH, -NH₂, alkyl such as methyl, or alkoxy such as methoxy and ethoxy.

[0065] Preferred G is hydrogen, C₁₋₃ aliphatic, or C_{1-C₃} aliphatic wherein one methylene unit of G is replaced by -C(O)-. More preferred G is hydrogen.

[0066] Preferred compounds of formula IIa are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of:

(a) R¹ is hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene chain and Ar¹ is a 6-membered saturated, partially saturated, or aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each member of R¹ is optionally substituted with one -Z-R³ and one to three additional groups independently selected from -CO₂R, -OR, halogen, -NRSO₂R, -SO₂N(R)₂, -NRCON(R)₂, -NO₂, or -N(R)₂;

(b) R² is Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar² is optionally substituted with one to five groups independently selected from -Z-R³, -R, halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R; and

(c) G is hydrogen.

[0067] More preferred compounds of formula IIa are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of:

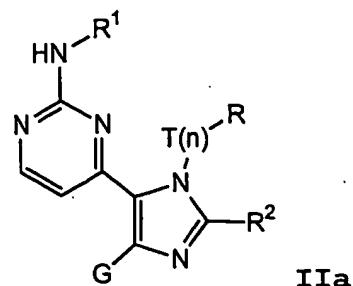
(a) R¹ is selected from a phenyl, benzyl, pyridyl, piperidinyl, or cyclohexyl ring, wherein said ring is optionally substituted with benzyloxy, phenoxy, -SO₂NH₂, -OH, -NO₂, -NH₂, -OMe, -Br, -Cl, -CO₂Me, -NHSO₂Me, 5 -NHSO₂Et, -NHCON(Me)₂, -NHCON(Et)₂, -NHCOPyrrolidin-1-yl, -NHCOmorpholin-4-yl, -O-CH₂-phenyl, -O(CH₂)₃OH, -O(CH₂)₃NH(CH₂)₂OH, -O(CH₂)₂NH(CH₂)₂OH, -O(CH₂)₃N(hydroxyethyl)(methyl), -O(CH₂)₃pyrrolidin-1-yl, -O(CH₂)₂morpholin-4-yl, -O(CH₂)₃N(Me)₂, -O(CH₂)₃N(Et)₂, 10 -O(CH₂)₃(4-hydroxyethyl piperazin-1-yl), -O(CH₂)₃piperazin-1-yl, -O(CH₂)₃(4-hydroxymethylpiperidin-1-yl), -O(CH₂)₃(4-hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂, -NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-aminothiazol-4-yl), -NHCOCH₂cyclopropyl, 15 -NHCO(CH₂)₂N(Et)₂, -NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl, -NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl;

(b) R² is selected from phenyl, pyridyl, 20 pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein R² is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo, fluoro, trifluoromethyl, -OH, -NH₂, methyl, methoxy, or ethoxy; and

(c) G is hydrogen.

30 [0068] Exemplary compounds of formula IIa are shown below in Table 1.

Table 1. Compounds of Formula IIa



No. IIa-	G	-T _(n) -R	R ¹	R ²
1	H	H	4-Cl-phenyl	Ph
2	H	H	4-F-phenyl	Ph
3	H	H	3-OMe-Ph	Ph
4	H	H	3,5-(OMe) ₂ -Ph	Ph
5	H	CH ₃	4-Cl-phenyl	pyridin-3-yl
6	H	CH ₃	4-F-phenyl	pyridin-3-yl
7	H	CH ₃	Ph	pyridin-3-yl
8	H	CH ₃	3-BnO-Ph	pyridin-3-yl
9	H	CH ₃	6-Cl-pyridin-3-yl	pyridin-3-yl
10	H	CH ₂ OCH ₃	4-Cl-phenyl	Ph
11	H	CH ₂ OCH ₃	4-F-phenyl	Ph
12	H	CH ₂ OCH ₃	Ph	Ph
13	H	CH ₂ OCH ₃	4-NO ₂ -Ph	Ph
14	H	CH ₂ OCH ₃	3-OMe-Ph	Ph
15	H	CH ₂ OCH ₃	3,5-(OMe) ₂ -Ph	Ph
16	H	CH ₂ OCH ₃	3-Br-Ph	Ph
17	H	CH ₂ OCH ₃	3-BnO-Ph	Ph
18	H	CH ₃	3-OMe-Ph	pyridin-3-yl
19	H	CH ₃	3,5-(OMe) ₂ -Ph	pyridin-3-yl
20	H	CH ₃	3-Br-Ph	pyridin-3-yl
21	H	CH ₃	4-NO ₂ -Ph	pyridin-3-yl
22	H	CH ₃	3-CO ₂ CH ₃ -Ph	pyridin-3-yl
23	H	H	4-Cl-Ph	-CH ₂ -(2,6-di-Cl)-Ph
24	H	H	4-F-Ph	-CH ₂ -(2,6-di-Cl)-Ph

No. IIa-	G	-T _(n) -R	R ¹	R ²
25	H	H	3-OMe-Ph	-CH ₂ -(2,6-di-Cl)-Ph
26	H	H	3,5-(OMe) ₂ -Ph	-CH ₂ -(2,6-di-Cl)-Ph
27	H	H	3-Br-Ph	-CH ₂ -(2,6-di-Cl)-Ph
28	H	H	Ph	-CH ₂ -(2,6-di-Cl)-Ph
29	H	H	3-BnO-Ph	-CH ₂ -(2,6-di-Cl)-Ph
30	H	H	4-NO ₂ -Ph	-CH ₂ -(2,6-di-Cl)-Ph
31	H	H	3-CO ₂ CH ₃ -Ph	-CH ₂ -(2,6-di-Cl)-Ph
32	H	H	6-Cl-pyridin-3-yl	-CH ₂ -(2,6-di-Cl)-Ph
33	H	H	cyclohexyl	-CH ₂ -(2,6-di-Cl)-Ph
34	H	CH ₂ OCH ₃	3-Cl-Ph	Ph
35	H	CH ₃	3-Cl-Ph	pyridin-3-yl
36	H	H	H	4-CO ₂ H-phenyl
37	H	H	H	4-Cl-phenyl
38	H	H	H	4-CF ₃ -phenyl
39	H	H	H	4-CH ₃ -phenyl
40	H	H	H	2-Cl-phenyl
41	H	H	H	4-OCH ₃ -phenyl
42	H	H	Ph	4-Cl-phenyl
43	H	H	Ph	4-CF ₃ -phenyl
44	H	H	Ph	4-CH ₃ -phenyl
45	H	H	CH ₂ Ph	pyridin-3-yl
46	H	H	COPh	4-Cl-phenyl
47	H	H	COPh	4-CF ₃ -phenyl
48	H	H	COPh	4-CH ₃ -phenyl
49	H	H	CONHCH ₂ Ph	4-Cl-phenyl
50	H	H	CONHCH ₂ Ph	4-CF ₃ -phenyl
51	H	H	CONHCH ₂ Ph	4-CH ₃ -phenyl
52	H	H	SO ₂ Me	CH ₂ Ph
53	H	H	Ph	thiazol-2-yl
54	H	H	cyclohexyl	piperidin-1-yl
55	H	H	cyclohexyl	4-CONHMe-phenyl

No. IIa-	G	-T _(n) -R	R ¹	R ²
56	H	H	Ph	Ph
57	H	H	CH ₂ Ph	CH ₂ Ph
58	H	H	H	CH ₂ Ph
59	H	H	H	Ph
60	H	H	3-OBn-Ph	Ph
61	H	H	3-SO ₂ NH ₂ -Ph	Ph
62	H	H	3-OH-Ph	Ph
63	H	H	4-OBn-Ph	Ph
64	H	H	3-NO ₂ -Ph	3-OMe-Ph
65	H	H	3-NH ₂ -Ph	3-OMe-Ph
66	H	H	3-NO ₂ -Ph	3-OH-Ph
67	H	H	Ph	3-OBn-Ph
68	H	H	3-NO ₂ -Ph	3-OBn-Ph
69	H	H	3-NO ₂ -Ph	3-OBn-Ph
70	H	H	3-OBn-Ph	3-pyridyl
71	H	H	3-OH-Ph	3-pyridyl
72	H	H	3-NH ₂ -Ph	3-Br-Ph
73	H	H	3-NH ₂ -Ph	3-OPh-Ph
74	H	H	3-OBn-Ph	5-Br-3-pyridyl
75	H	H	Ph	3-OPh-Ph
76	H	H	3-OH-Ph	3-OBn-Ph
77	H	H	3-OH-Ph	3-OPh-Ph
78	H	H	3-OH-Ph	3-OH-Ph
79	H	H	3-OH-Ph	3-Br-Ph
80	H	H	3-OBn-Ph	3-Br-Ph
81	H	H	3-OH-Ph	3-(3-OH-Ph)-Ph
82	H	H	3-OH-Ph	3-(3-OEt-Ph)-Ph
83	H	H	3-OH-Ph	3-(3-pyridyl)-Ph
84	H	H	3-OBn-Ph	5-Ph-pyridin-3-yl
85	H	H	3-OBn-Ph	5-Br-3-pyridyl
86	H	H	3-OBn-Ph	5-Ph-3-pyridyl

No. IIa-	G	-T _(a) -R	R ¹	R ²
87	H	H	4-OH-Ph	Ph
88	H	H	3-OH-Ph	5-Ph-pyridin-3-yl
89	H	H	3-OH-Ph	3-(3-NH ₂ -Ph)-Ph
90	H	H	3-OH-Ph	3-(3-Cl, 4-F-Ph)-Ph
91	H	H	3-OH-Ph	3-(4-iPr-Ph)-Ph
92	H	H	3-NO ₂ -Ph	5-Ph-pyridin-3-yl
93	H	H	3-OH-Ph	3-(3-N-Boc-pyrrol-2-yl)-Ph
94	H	H	3-NHSO ₂ Me-Ph	3-pyridyl
95	H	H	3-NHSO ₂ Et-Ph	3-pyridyl
96	H	H	3-SO ₂ NH ₂ -Ph	3-pyridyl
97	H	H	3-OH-Ph	3-(2-OH-Ph)-Ph
98	H	H	3-OH-Ph	3-(3-pyrrol-2-yl)-Ph
99	H	H	3-OH-Ph	3-(6-OMe-pyridin-2-yl)-Ph
100	H	H	3-OH-Ph	3-(5-OMe-pyridin-2-yl)-Ph
101	H	H	3-OH-Ph	3-(2,5-Me ₂ -isoxazol-4-yl)-Ph
102	H	H	3-OH-Ph	3-(pyridin-4-yl)-Ph
103	H	CH ₃	H	4-CO ₂ H-phenyl
104	H	CH ₃	H	4-Cl-phenyl
105	H	CH ₃	H	4-CF ₃ -phenyl
106	H	CH ₃	H	4-CH ₃ -phenyl
107	H	CH ₃	H	2-Cl-phenyl
108	H	CH ₃	H	4-OCH ₃ -phenyl
109	H	CH ₃	Ph	4-Cl-phenyl
110	H	CH ₃	Ph	4-CF ₃ -phenyl
111	H	CH ₃	Ph	4-CH ₃ -phenyl
112	H	CH ₃	CH ₂ Ph	pyridin-3-yl
113	H	CH ₃	COPh	4-Cl-phenyl
114	H	CH ₃	COPh	4-CF ₃ -phenyl
115	H	CH ₃	COPh	4-CH ₃ -phenyl
116	H	CH ₃	CONHCH ₂ Ph	4-Cl-phenyl

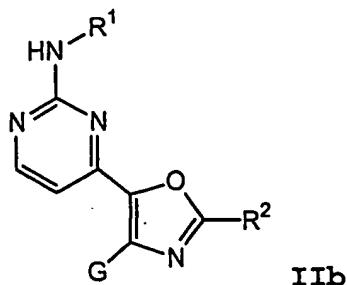
No. IIa-	G	-T _(n) -R	R ¹	R ²
117	H	CH ₃	CONHCH ₂ Ph	4-CF ₃ -phenyl
118	H	CH ₃	CONHCH ₂ Ph	4-CH ₃ -phenyl
119	H	CH ₃	SO ₂ Me	CH ₂ Ph
120	H	CH ₃	Ph	thiazol-2-yl
121	H	CH ₃	cyclohexyl	piperidin-1-yl
122	H	CH ₃	cyclohexyl	4-CONHMe-phenyl
123	H	CH ₃	Ph	Ph
124	H	CH ₃	CH ₂ Ph	CH ₂ Ph
125	H	CH ₃	H	CH ₂ Ph
126	H	CH ₃	H	Ph
127	H	CH ₃	3-OBn-Ph	Ph
128	H	CH ₃	3-SO ₂ NH ₂ -Ph	Ph
129	H	CH ₃	3-OH-Ph	Ph
130	H	CH ₃	4-OBn-Ph	Ph
131	H	CH ₃	3-NO ₂ -Ph	3-OMe-Ph
132	H	CH ₃	3-NH ₂ -Ph	3-OMe-Ph
133	H	CH ₃	3-NO ₂ -Ph	3-OH-Ph
134	H	CH ₃	Ph	3-OBn-Ph
135	H	CH ₃	3-NO ₂ -Ph	3-OBn-Ph
136	H	CH ₃	3-NO ₂ -Ph	3-OBn-Ph
137	H	CH ₃	3-OH-Ph	3-pyridyl
138	H	CH ₃	3-NH ₂ -Ph	3-Br-Ph
139	H	CH ₃	3-NH ₂ -Ph	3-OPh-Ph
140	H	CH ₃	3-OBn-Ph	5-Br-3-pyridyl
141	H	CH ₃	Ph	3-OPh-Ph
142	H	CH ₃	3-OH-Ph	3-OBn-Ph
143	H	CH ₃	3-OH-Ph	3-OPh-Ph
144	H	CH ₃	3-OH-Ph	3-OH-Ph
145	H	CH ₃	3-OH-Ph	3-Br-Ph
146	H	CH ₃	3-OBn-Ph	3-Br-Ph
147	H	CH ₃	3-OH-Ph	3-(3-OH-Ph)-Ph

No. IIa-	G	-T _(n) -R	R ¹	R ²
148	H	CH ₃	3-OH-Ph	3-(3-OEt-Ph)-Ph
149	H	CH ₃	3-OH-Ph	3-(3-pyridyl)-Ph
150	H	CH ₃	3-OBn-Ph	5-Ph-pyridin-3-yl
151	H	CH ₃	3-OBn-Ph	5-Br-3-pyridyl
152	H	CH ₃	3-OBn-Ph	5-Ph-3-pyridyl
153	H	CH ₃	4-OH-Ph	Ph
154	H	CH ₃	3-OH-Ph	5-Ph-pyridin-3-yl
155	H	CH ₃	3-OH-Ph	3-(3-NH ₂ -Ph)-Ph
156	H	CH ₃	3-OH-Ph	3-(3-Cl, 4-F-Ph)-Ph
157	H	CH ₃	3-OH-Ph	3-(4-iPr-Ph)-Ph
158	H	CH ₃	3-NO ₂ -Ph	5-Ph-pyridin-3-yl
159	H	CH ₃	3-OH-Ph	3-(3-N-Boc-pyrrol-2-yl)-Ph
160	H	CH ₃	3-NHSO ₂ Me-Ph	3-pyridyl
161	H	CH ₃	3-NHSO ₂ Et-Ph	3-pyridyl
162	H	CH ₃	3-OMe-Ph	Ph
163	H	CH ₃	3-SO ₂ NH ₂ -Ph	3-pyridyl
164	H	CH ₃	3-OH-Ph	3-(2-OH-Ph)-Ph
165	H	CH ₃	3-OH-Ph	3-(3-pyrrol-2-yl)-Ph
166	H	CH ₃	3-OH-Ph	3-(6-OMe-pyridin-2-yl)-Ph
167	H	CH ₃	3-OH-Ph	3-(5-OMe-pyridin-2-yl)-Ph
168	H	CH ₃	3-OH-Ph	3-(2,5-Me ₂ -isoxazol-4-yl)-Ph
169	H	CH ₃	3-OH-Ph	3-(pyridin-4-yl)-Ph
170	H	CH ₂ OCH ₃	H	4-CO ₂ H-phenyl
171	H	CH ₂ OCH ₃	H	4-Cl-phenyl
172	H	CH ₂ OCH ₃	H	4-CF ₃ -phenyl
173	H	CH ₂ OCH ₃	H	4-CH ₃ -phenyl
174	H	CH ₂ OCH ₃	H	2-Cl-phenyl
175	H	CH ₂ OCH ₃	H	4-OCH ₃ -phenyl
176	H	CH ₂ OCH ₃	Ph	4-Cl-phenyl
177	H	CH ₂ OCH ₃	Ph	4-CF ₃ -phenyl

No. IIa-	G	-T _(n) -R	R ¹	R ²
178	H	CH ₂ OCH ₃	Ph	4-CH ₃ -phenyl
179	H	CH ₂ OCH ₃	CH ₂ Ph	pyridin-3-yl
180	H	CH ₂ OCH ₃	COPh	4-Cl-phenyl
181	H	CH ₂ OCH ₃	COPh	4-CF ₃ -phenyl
182	H	CH ₂ OCH ₃	COPh	4-CH ₃ -phenyl
183	H	CH ₂ OCH ₃	CONHCH ₂ Ph	4-Cl-phenyl
184	H	CH ₂ OCH ₃	CONHCH ₂ Ph	4-CF ₃ -phenyl
185	H	CH ₂ OCH ₃	CONHCH ₂ Ph	4-CH ₃ -phenyl
186	H	CH ₂ OCH ₃	SO ₂ Me	CH ₂ Ph
187	H	CH ₂ OCH ₃	Ph	thiazol-2-yl
188	H	CH ₂ OCH ₃	cyclohexyl	piperidin-1-yl
189	H	CH ₂ OCH ₃	cyclohexyl	4-COHNMe-phenyl
190	H	CH ₂ OCH ₃	CH ₂ Ph	CH ₂ Ph
191	H	CH ₂ OCH ₃	H	CH ₂ Ph
192	H	CH ₂ OCH ₃	H	Ph
193	H	CH ₂ OCH ₃	3-SO ₂ NH ₂ -Ph	Ph
194	H	CH ₂ OCH ₃	3-OH-Ph	Ph
195	H	CH ₂ OCH ₃	4-OBn-Ph	Ph
196	H	CH ₂ OCH ₃	3-NO ₂ -Ph	3-OMe-Ph
197	H	CH ₂ OCH ₃	3-NH ₂ -Ph	3-OMe-Ph
198	H	CH ₂ OCH ₃	3-NO ₂ -Ph	3-OH-Ph
199	H	CH ₂ OCH ₃	Ph	3-OBn-Ph
200	H	CH ₂ OCH ₃	3-NO ₂ -Ph	3-OBn-Ph
201	H	CH ₂ OCH ₃	3-NO ₂ -Ph	3-OBn-Ph
202	H	CH ₂ OCH ₃	3-OBn-Ph	3-pyridyl
203	H	CH ₂ OCH ₃	3-OH-Ph	3-pyridyl
204	H	CH ₂ OCH ₃	3-NH ₂ -Ph	3-Br-Ph
205	H	CH ₂ OCH ₃	3-NH ₂ -Ph	3-OPh-Ph
206	H	CH ₂ OCH ₃	3-OBn-Ph	5-Br-3-pyridyl
207	H	CH ₂ OCH ₃	Ph	3-OPh-Ph
208	H	CH ₂ OCH ₃	3-OH-Ph	3-OBn-Ph

No. IIa-	G	-T _(n) -R	R ¹	R ²
209	H	CH ₂ OCH ₃	3-OH-Ph	3-OPh-Ph
210	H	CH ₂ OCH ₃	3-OH-Ph	3-OH-Ph
211	H	CH ₂ OCH ₃	3-OH-Ph	3-Br-Ph
212	H	CH ₂ OCH ₃	3-OBn-Ph	3-Br-Ph
213	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-OH-Ph)-Ph
214	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-OEt-Ph)-Ph
215	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-pyridyl)-Ph
216	H	CH ₂ OCH ₃	3-OBn-Ph	5-Ph-pyridin-3-yl
217	H	CH ₂ OCH ₃	3-OBn-Ph	5-Br-3-pyridyl
218	H	CH ₂ OCH ₃	3-OBn-Ph	5-Ph-3-pyridyl
219	H	CH ₂ OCH ₃	4-OH-Ph	Ph
220	H	CH ₂ OCH ₃	3-OH-Ph	5-Ph-pyridin-3-yl
221	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-NH ₂ -Ph)-Ph
222	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-Cl, 4-F-Ph)-Ph
223	H	CH ₂ OCH ₃	3-OH-Ph	3-(4-iPr-Ph)-Ph
224	H	CH ₂ OCH ₃	3-NO ₂ -Ph	5-Ph-pyridin-3-yl
225	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-N-Boc-pyrrol-2-yl)-Ph
226	H	CH ₂ OCH ₃	3-NHSO ₂ Me-Ph	3-pyridyl
227	H	CH ₂ OCH ₃	3-NHSO ₂ Et-Ph	3-pyridyl
228	H	CH ₂ OCH ₃	3-SO ₂ NH ₂ -Ph	3-pyridyl
229	H	CH ₂ OCH ₃	3-OH-Ph	3-(2-OH-Ph)-Ph
230	H	CH ₂ OCH ₃	3-OH-Ph	3-(3-pyrrol-2-yl)-Ph
231	H	CH ₂ OCH ₃	3-OH-Ph	3-(6-OMe-pyridin-2-yl)-Ph
232	H	CH ₂ OCH ₃	3-OH-Ph	3-(5-OMe-pyridin-2-yl)-Ph
233	H	CH ₂ OCH ₃	3-OH-Ph	3-(2,5-Me ₂ -isoxazol-4-yl)-Ph
234	H	CH ₂ OCH ₃	3-OH-Ph	3-(pyridin-4-yl)-Ph

[0069] Another embodiment related to compounds of formula IIb:



or a pharmaceutically acceptable derivative thereof,
wherein R¹, R², and G are as described above.

[0070] Preferred R¹ groups of formula **IIb** are selected
5 from hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene
chain and Ar¹ is an optionally substituted 6-membered
saturated, partially saturated, or aryl ring having zero
to two heteroatoms independently selected from nitrogen,
oxygen, or sulfur. More preferred R¹ groups of formula
10 **IIa** are selected from phenyl, benzyl, pyridyl,
piperidinyl, or cyclohexyl. Preferred substituents on R¹
are selected from -CO₂R, -OR, -Z-R³, halogen, -NRSO₂R,
-SO₂N(R)₂, -NRCON(R)₂, -NO₂, or -N(R)₂. More preferred
substituents of R¹ are selected from benzyloxy, phenoxy,
15 -SO₂NH₂, -OH, -NO₂, -NH₂, -OMe, -Br, -Cl, -CO₂Me, -NHSO₂Me,
-NHSO₂Et, -NHCON(Me)₂, -NHCON(Et)₂, -NHCOpyrrolidin-1-yl,
or -NHCOMorpholin-4-yl.

[0071] Preferred R² groups of formula **IIb** are selected
from Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6
20 membered ring selected from carbocyclic, aryl, or a
heterocyclyl or heteroaryl ring having one to two
heteroatoms independently selected from nitrogen, oxygen
or sulfur, wherein Ar² is optionally substituted with one
to five groups independently selected from -Z-R³, -R,
25 halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R,
-NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂,
-OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R,
-N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R. More

preferred R² groups of formula IIb are selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl. Preferred Z is a C₁₋₄ alkylidene chain and wherein one methylene unit of Z is optionally replaced by -S-, -O-, -N(R)-, or -C(O)O-. Preferred substituents on Ar² are selected from -Z-Ar³, -R, halogen, -OR, -N(R)₂, or -CO₂R, wherein Ar³ is an optionally substituted 5-6 membered aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur. More preferred substituents on Ar² are selected from phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 15 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, halogen such as chloro, bromo, and fluoro, haloalkyl such as trifluoromethyl, -OH, -NH₂, alkyl such as methyl, or alkoxy such as methoxy and ethoxy.

[0072] Preferred G is hydrogen, C₁₋₃ aliphatic, or C_{1-C₃} aliphatic wherein one methylene unit of G is replaced by -C(O)-. More preferred G is hydrogen.

[0073] Preferred compounds of formula IIb are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of:

(a) R¹ is hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene chain and Ar¹ is a 6-membered saturated, partially saturated, or aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each member of R¹ is optionally substituted with one -Z-R³ and one to three additional groups independently selected from -CO₂R, -OR, halogen, -NRSO₂R, -SO₂N(R)₂, -NRCON(R)₂, -NO₂, or -N(R)₂;

- 40 -

(b) R² is Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar² is optionally substituted with one to five groups independently selected from -Z-R³, -R, halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NR₂O₂R, -C(O)R, -CO₂R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R, 10 -N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R; and

(c) G is hydrogen.

[0074] More preferred compounds of formula IIb are those having one or more, more preferably more than one, and most preferably all, of the features selected from 15 the group consisting of:

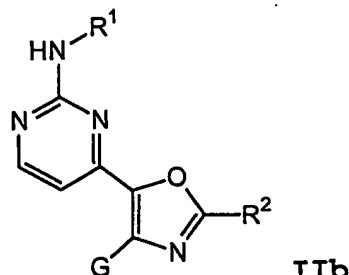
(a) R¹ is selected from a phenyl, benzyl, pyridyl, piperidinyl, or cyclohexyl ring, wherein said ring is optionally substituted with benzyloxy, phenoxy, -SO₂NH₂, -OH, -NO₂, -NH₂, -OMe, -Br, -Cl, -CO₂Me, -NHSO₂Me, 20 -NHSO₂Et, -NHCON(Me)₂, -NHCON(Et)₂, -NHCOpiperidin-1-yl, -NHCOpiperazin-4-yl, -O-CH₂-phenyl, -O(CH₂)₃OH, -O(CH₂)₃NH(CH₂)₂OH, -O(CH₂)₂NH(CH₂)₂OH, -O(CH₂)₃N(hydroxyethyl)(methyl), -O(CH₂)₃pyrrolidin-1-yl, -O(CH₂)₂morpholin-4-yl, -O(CH₂)₃N(Me)₂, -O(CH₂)₃N(Et)₂, 25 -O(CH₂)₃(4-hydroxyethyl)piperazin-1-yl, -O(CH₂)₃piperazin-1-yl, -O(CH₂)₃(4-hydroxymethyl)piperidin-1-yl, -O(CH₂)₃(4-hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂, -NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-aminothiazol-4-yl), -NHCOCH₂cyclopropyl, -NHCO(CH₂)₂N(Et)₂, 30 -NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl, -NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl;

(b) R² is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein R² is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 5 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo, fluoro, trifluoromethyl, -OH, 10 -NH₂, methyl, methoxy, or ethoxy; and

(c) G is hydrogen.

[0075] Exemplary compounds of formula IIb are shown below in Table 2.

Table 2. Compounds of Formula IIb



15

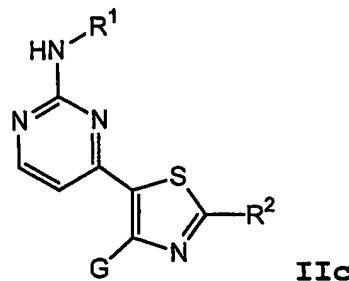
No. IIb-	G	R ¹	R ²
1	H	4-Cl-phenyl	Ph
2	H	4-F-phenyl	Ph
3	H	3-OMe-Ph	Ph
4	H	3,5-(OMe) ₂ -Ph	Ph
5	H	Ph	Ph
6	H	3-BnO-Ph	Ph
7	H	4-NO ₂ -Ph	Ph
8	H	3-Br-Ph	Ph
9	H	3-CO ₂ CH ₃ -Ph	Ph
10	H	cyclohexyl	Ph
11	H	4-Cl-phenyl	2-OBn-Ph
12	H	3-NO ₂ -Ph	2-OBn-Ph

No. IIb-	G	R ¹	R ²
13	H	CH ₂ -phenyl	2-OBn-Ph
14	H	cyclohexyl	2-OBn-Ph
15	H	3-OMe-Ph	2-OBn-Ph
16	H	3,5-(OMe) ₂ -Ph	2-OBn-Ph
17	H	4-Cl-phenyl	cyclohexyl
18	H	3-Cl-phenyl	Ph
19	H	H	4-CO ₂ H-phenyl
20	H	H	4-Cl-phenyl
21	H	H	4-CF ₃ -phenyl
22	H	H	4-CH ₃ -phenyl
23	H	H	2-Cl-phenyl
24	H	H	4-OCH ₃ -phenyl
25	H	Ph	4-Cl-phenyl
26	H	Ph	4-CF ₃ -phenyl
27	H	Ph	4-CH ₃ -phenyl
28	H	CH ₂ Ph	pyridin-3-yl
29	H	COPh	4-Cl-phenyl
30	H	COPh	4-CF ₃ -phenyl
31	H	COPh	4-CH ₃ -phenyl
32	H	CONHCH ₂ Ph	4-Cl-phenyl
33	H	CONHCH ₂ Ph	4-CF ₃ -phenyl
34	H	CONHCH ₂ Ph	4-CH ₃ -phenyl
35	H	SO ₂ Me	CH ₂ Ph
36	H	Ph	thiazol-2-yl
37	H	cyclohexyl	piperidin-1-yl
38	H	cyclohexyl	4-CONHMe-phenyl
39	H	CH ₂ Ph	CH ₂ Ph
40	H	H	CH ₂ Ph
41	H	H	Ph
42	H	3-SO ₂ NH ₂ -Ph	Ph
43	H	3-OH-Ph	Ph

No. IIb-	G	R ¹	R ²
44	H	4-OBn-Ph	Ph
45	H	3, 5-(OMe) ₂ -Ph	cyclohexyl
46	H	3-SO ₂ NH ₂ -Ph	cyclohexyl
47	H	3-OBn-Ph	cyclohexyl
48	H	Ph	cyclohexyl
49	H	4-CO ₂ Et-Ph	cyclohexyl
50	H	3-OH-Ph	cyclohexyl
51	H	3-NO ₂ -Ph	3-OMe-Ph
52	H	3-NH ₂ -Ph	3-OMe-Ph
53	H	3-NO ₂ -Ph	3-OH-Ph
54	H	Ph	3-OBn-Ph
55	H	3-NO ₂ -Ph	3-OBn-Ph
56	H	3-NO ₂ -Ph	3-OBn-Ph
57	H	3-OBn-Ph	3-pyridyl
58	H	3-OH-Ph	3-pyridyl
59	H	3-NH ₂ -Ph	3-Br-Ph
60	H	3-NH ₂ -Ph	3-OPh-Ph
61	H	3-OBn-Ph	5-Br-3-pyridyl
62	H	Ph	3-OPh-Ph
63	H	3-OH-Ph	3-OBn-Ph
64	H	3-OH-Ph	3-OPh-Ph
65	H	3-OH-Ph	3-OH-Ph
66	H	3-OH-Ph	3-Br-Ph
67	H	3-OBn-Ph	3-Br-Ph
68	H	3-OH-Ph	3-(3-OH-Ph)-Ph
69	H	3-OH-Ph	3-(3-OEt-Ph)-Ph
70	H	3-OH-Ph	3-(3-pyridyl)-Ph
71	H	3-OBn-Ph	5-Ph-pyridin-3-yl
72	H	3-OBn-Ph	5-Br-3-pyridyl
73	H	3-OBn-Ph	5-Ph-3-pyridyl
74	H	4-OH-Ph	Ph

No. IIb-	G	R ¹	R ²
75	H	3-OH-Ph	5-Ph-pyridin-3-yl
76	H	3-OH-Ph	3-(3-NH ₂ -Ph)-Ph
77	H	3-OH-Ph	3-(3-Cl, 4-F-Ph)-Ph
78	H	3-OH-Ph	3-(4-iPr-Ph)-Ph
79	H	3-NO ₂ -Ph	5-Ph-pyridin-3-yl
80	H	3-OH-Ph	3-(3-N-Boc-pyrrol-2-yl)-Ph
81	H	3-NHSO ₂ Me-Ph	3-pyridyl
82	H	3-NHSO ₂ Et-Ph	3-pyridyl
83	H	3-SO ₂ NH ₂ -Ph	3-pyridyl
84	H	3-OH-Ph	3-(2-OH-Ph)-Ph
85	H	3-OH-Ph	3-(3-pyrrol-2-yl)-Ph
86	H	3-OH-Ph	3-(6-OMe-pyridin-2-yl)-Ph
87	H	3-OH-Ph	3-(5-OMe-pyridin-2-yl)-Ph
88	H	3-OH-Ph	3-(2,5-Me ₂ -isoxazol-4-yl)-Ph
89	H	3-OH-Ph	3-(pyridin-4-yl)-Ph

[0076] Another embodiment related to compounds of formula IIc:



5 or a pharmaceutically acceptable derivative thereof, wherein R¹, R², and G are as described above.

[0077] Preferred R¹ groups of formula IIc are selected from hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene chain and Ar¹ is an optionally substituted 6-membered saturated, partially saturated, or aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur. More preferred R¹ groups of formula

IIC are selected from phenyl, benzyl, pyridyl, piperidinyl, or cyclohexyl. Preferred substituents on R¹ are selected from -CO₂R, -OR, -Z-R³, halogen, -NRSO₂R, -SO₂N(R)₂, -NRCON(R)₂, -NO₂, or -N(R)₂. More preferred substituents of R¹ are selected from benzyloxy, phenoxy, -SO₂NH₂, -OH, -NO₂, -NH₂, -OMe, -Br, -Cl, -CO₂Me, -NHSO₂Me, -NHSO₂Et, -NHCON(Me)₂, -NHCON(Et)₂, -NHCOPyrrolidin-1-yl, or -NHCOMorpholin-4-yl.

[0078] Preferred R² groups of formula **IIC** are selected from Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, wherein Ar² is optionally substituted with one to five groups independently selected from -Z-R³, -R, halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R. More preferred R² groups of formula **IIC** are selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl. Preferred Z is a C₁₋₄ alkylidene chain and wherein one methylene unit of Z is optionally replaced by -S-, -O-, -N(R)-, or -C(O)O-. Preferred substituents on Ar² are selected from -Z-Ar³, -R, halogen, -OR, -N(R)₂, or -CO₂R, wherein Ar³ is an optionally substituted 5-6 membered aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur. More preferred substituents on Ar² are selected from phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl,

4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, halogen such as chloro, bromo, and fluoro, haloalkyl such as trifluoromethyl, -OH, -NH₂, alkyl such as methyl, or alkoxy such as methoxy and ethoxy.

5 [0079] Preferred G is hydrogen, C₁₋₃ aliphatic, or C_{1-C₃} aliphatic wherein one methylene unit of G is replaced by -C(O)-. More preferred G is hydrogen.

10 [0080] Preferred compounds of formula IIc are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of:

15 (a) R¹ is hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene chain and Ar¹ is a 6-membered saturated, partially saturated, or aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each member of R¹ is optionally substituted with one -Z-R³ and one to three additional groups independently selected from -CO₂R, -OR, halogen, -NRSO₂R, -SO₂N(R)₂, -NRCON(R)₂, -NO₂, or -N(R)₂;

20 (b) R² is Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar² is optionally substituted with one to five groups independently selected from -Z-R³, -R, halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NR₂CO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R; and

25 (c) G is hydrogen.

[0081] More preferred compounds of formula IIc are those having one or more, more preferably more than one,

and most preferably all, of the features selected from the group consisting of:

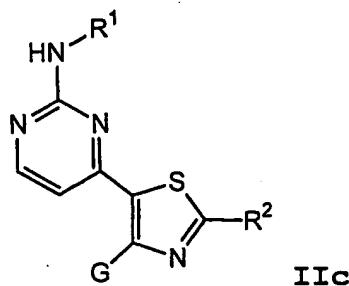
(a) R¹ is selected from a phenyl, benzyl, pyridyl, piperidinyl, or cyclohexyl ring, wherein said ring is 5 optionally substituted with benzyloxy, phenoxy, -SO₂NH₂, -OH, -NO₂, -NH₂, -OMe, -Br, -Cl, -CO₂Me, -NHSO₂Me, -NHSO₂Et, -NHCON(Me)₂, -NHCON(Et)₂, -NHCOPyrrolidin-1-yl, -NHCOMorpholin-4-yl, -O-CH₂-phenyl, -O(CH₂)₃OH, -O(CH₂)₃NH(CH₂)₂OH, -O(CH₂)₂NH(CH₂)₂OH, 10 -O(CH₂)₃N(hydroxyethyl)(methyl), -O(CH₂)₃pyrrolidin-1-yl, -O(CH₂)₂morpholin-4-yl, -O(CH₂)₃N(Me)₂, -O(CH₂)₃N(Et)₂, -O(CH₂)₃(4-hydroxyethyl piperazin-1-yl), -O(CH₂)₃piperazin-1-yl, -O(CH₂)₃(4-hydroxymethylpiperidin-1-yl), -O(CH₂)₃(4-hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂, 15 -NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-aminothiazol-4-yl), -NHCOCH₂cyclopropyl, -NHCO(CH₂)₂N(Et)₂, -NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl, -NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-20 yl;

(b) R² is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein R² is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo, fluoro, trifluoromethyl, -OH, -NH₂, methyl, methoxy, or ethoxy; and

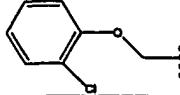
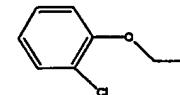
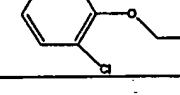
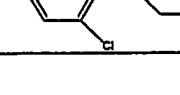
(c) G is hydrogen.

[0082] Exemplary compounds of formula IIc are shown below in Table 3.

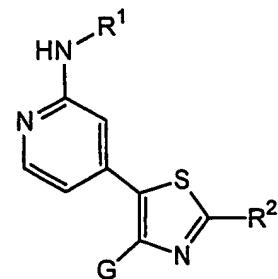
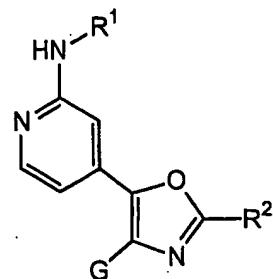
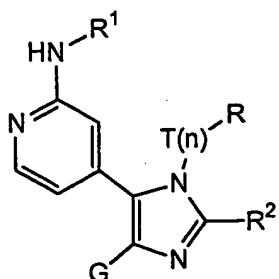
Table 3. Compounds of Formula IIc



No. IIc-	G	R ¹	R ²
1	H	cyclohexyl	Ph
2	H	cyclohexyl	2-OBn-Ph
3	H	H	4-CO ₂ H-phenyl
4	H	H	4-Cl-phenyl
5	H	H	4-CF ₃ -phenyl
6	H	H	4-CH ₃ -phenyl
7	H	H	2-Cl-phenyl
8	H	H	4-OCH ₃ -phenyl
9	H	CH ₂ Ph	pyridin-3-yl
10	H	COPh	4-Cl-phenyl
11	H	COPh	4-CF ₃ -phenyl
12	H	COPh	4-CH ₃ -phenyl
13	H	CONHCH ₂ Ph	4-Cl-phenyl
14	H	CONHCH ₂ Ph	4-CF ₃ -phenyl
15	H	CONHCH ₂ Ph	4-CH ₃ -phenyl
16	H	SO ₂ Me	CH ₂ Ph
17	H	cyclohexyl	piperidin-1-yl
18	H	cyclohexyl	4-CONHMe-phenyl
19	H	CH ₂ Ph	CH ₂ Ph
20	H	H	CH ₂ Ph
21	H	H	Ph
22	CH ₃	4-SO ₂ NH ₂ -Ph	thiophen-2-yl
23	CH ₃	4-F-Ph	thiophen-2-yl
24	CH ₃	4-Cl-Ph	thiophen-2-yl

No. IIc-	G	R ¹	R ²
25	CH ₃	4-NO ₂ -Ph	thiophen-2-yl
26	CH ₃	H	
27	CH ₃	Ph	Ph
28	CH ₃	4-F-Ph	Ph
29	CH ₃	4-Cl-Ph	Ph
30	CH ₃	3-Cl-Ph	Ph
31	CH ₃	4-NO ₂ -Ph	Ph
32	CH ₃	3-OBn-Ph	Ph
33	CH ₃	Ph	4-Cl-Ph
34	CH ₃	4-F-Ph	4-Cl-Ph
35	CH ₃	4-Cl-Ph	4-Cl-Ph
36	CH ₃	3-Cl-Ph	4-Cl-Ph
37	CH ₃	3-BnO-Ph	4-Cl-Ph
38	CO ₂ Et	4-NO ₂ -Ph	Ph
39	CH ₃	Ph	
40	CH ₃	4-F-Ph	
41	CH ₃	4-Cl-Ph	
42	CH ₃	3-Cl-Ph	
43	CH ₃	3-BnO-Ph	

[0083] The above formulae IIa, IIb, and IIc compounds are those having a pyrimidine ring. Compounds of formula I having a pyridine ring are represented by the following 5 general formulae IIIa, IIIb, and IIIc shown below in Table 4.

Table 4. Formulae IIIa, IIIb, and IIIc

[0084] The compounds shown above in Table 4 are
5 structurally similar to compounds of formula IIa, IIb,
and IIc where the pyrimidine ring of formula IIa is
replaced by a pyridine (IIIa, IIIb, and IIIc).

Accordingly, preferred R¹, R², n, T, R, and G groups of
the compounds shown above in Table 4 are as described
10 above for the formula IIa, IIb or IIc compounds.

[0085] Exemplary structures of formulae IIIa, IIIb and
IIIc are set forth in Table 5 below.

Table 5. Compounds of Formulae IIIa, IIIb, and IIIc

No.	G	-T _(n) -R	R ¹	R ²
IIIa-1	H	H	4-Cl-phenyl	Ph
IIIa-2	H	H	4-F-phenyl	Ph
IIIa-3	H	H	3-OMe-Ph	Ph
IIIa-4	H	H	3,5-(OMe) ₂ -Ph	Ph
IIIa-5	H	CH ₃	4-Cl-phenyl	pyridin-3-yl
IIIa-6	H	CH ₃	4-F-phenyl	pyridin-3-yl
IIIa-7	H	CH ₃	Ph	pyridin-3-yl
IIIa-8	H	CH ₃	3-BnO-Ph	pyridin-3-yl
IIIa-9	H	CH ₃	6-Cl-pyridin-3-yl	pyridin-3-yl
IIIa-10	H	CH ₂ OCH ₃	4-Cl-phenyl	Ph
IIIa-11	H	CH ₂ OCH ₃	4-F-phenyl	Ph
IIIa-12	H	CH ₂ OCH ₃	Ph	Ph
IIIa-13	H	CH ₂ OCH ₃	4-NO ₂ -Ph	Ph
IIIa-14	H	CH ₂ OCH ₃	3-OMe-Ph	Ph

No.	G	-T _(n) -R	R ¹	R ²
IIIa-15	H	CH ₂ OCH ₃	3,5-(OMe) ₂ -Ph	Ph
IIIa-16	H	CH ₂ OCH ₃	3-Br-Ph	Ph
IIIa-17	H	CH ₂ OCH ₃	3-BnO-Ph	Ph
IIIa-18	H	CH ₃	3-OMe-Ph	pyridin-3-yl
IIIa-19	H	CH ₃	3,5-(OMe) ₂ -Ph	pyridin-3-yl
IIIa-20	H	CH ₃	3-Br-Ph	pyridin-3-yl
IIIa-21	H	CH ₃	4-NO ₂ -Ph	pyridin-3-yl
IIIa-22	H	CH ₃	3-CO ₂ CH ₃ -Ph	pyridin-3-yl
IIIa-23	H	H	4-Cl-Ph	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-24	H	H	4-F-Ph	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-25	H	H	3-OMe-Ph	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-26	H	H	3,5-(OMe) ₂ -Ph	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-27	H	H	3-Br-Ph	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-28	H	H	Ph	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-29	H	H	3-BnO-Ph	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-30	H	H	4-NO ₂ -Ph	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-31	H	H	3-CO ₂ CH ₃ -Ph	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-32	H	H	6-Cl-pyridin-3-yl	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-33	H	H	cyclohexyl	-CH ₂ -(2,6-di-Cl)-Ph
IIIa-34	H	CH ₂ OCH ₃	3-Cl-Ph	Ph
IIIa-35	H	CH ₃	3-Cl-Ph	pyridin-3-yl
IIIa-36	H	H	H	4-CO ₂ H-phenyl
IIIa-37	H	H	H	4-Cl-phenyl
IIIa-38	H	H	H	4-CF ₃ -phenyl
IIIa-39	H	H	H	4-CH ₃ -phenyl
IIIa-40	H	H	H	2-Cl-phenyl
IIIa-41	H	H	H	4-OCH ₃ -phenyl
IIIa-42	H	H	H	4-CF ₃ -phenyl
IIIa-43	H	H	H	2-Cl-phenyl
IIIa-44	H	H	H	4-OCH ₃ -phenyl
IIIa-45	H	H	Ph	4-Cl-phenyl

No.	G	-T _(n) -R	R ¹	R ²
IIIa-46	H	H	Ph	4-Cl-phenyl
IIIa-47	H	H	Ph	4-CF ₃ -phenyl
IIIa-48	H	H	Ph	4-CF ₃ -phenyl
IIIa-49	H	H	Ph	4-CH ₃ -phenyl
IIIa-50	H	H	Ph	4-CH ₃ -phenyl
IIIa-51	H	H	CH ₂ Ph	pyridin-3-yl
IIIa-52	H	H	COPh	CONHCH ₂ Ph
IIIa-53	H	H	SO ₂ Me	CH ₂ Ph
IIIa-54	H	H	Ph	thiazol-2-yl
IIIa-55	H	H	cyclohexyl	piperidin-1-yl
IIIa-56	H	H	cyclohexyl	4-CONHMe-phenyl
IIIa-57	H	CH ₃	H	4-CO ₂ H-phenyl
IIIa-58	H	CH ₃	H	4-Cl-phenyl
IIIa-59	H	CH ₃	H	4-CF ₃ -phenyl
IIIa-60	H	CH ₃	H	4-CH ₃ -phenyl
IIIa-61	H	CH ₃	H	2-Cl-phenyl
IIIa-62	H	CH ₃	H	4-OCH ₃ -phenyl
IIIa-63	H	CH ₃	H	4-CF ₃ -phenyl
IIIa-64	H	CH ₃	H	2-Cl-phenyl
IIIa-65	H	CH ₃	H	4-OCH ₃ -phenyl
IIIa-66	H	CH ₃	Ph	4-Cl-phenyl
IIIa-67	H	CH ₃	Ph	4-Cl-phenyl
IIIa-68	H	CH ₃	Ph	4-CF ₃ -phenyl
IIIa-69	H	CH ₃	Ph	4-CF ₃ -phenyl
IIIa-70	H	CH ₃	Ph	4-CH ₃ -phenyl
IIIa-71	H	CH ₃	Ph	4-CH ₃ -phenyl
IIIa-72	H	CH ₃	CH ₂ Ph	pyridin-3-yl
IIIa-73	H	CH ₃	COPh	CONHCH ₂ Ph
IIIa-74	H	CH ₃	SO ₂ Me	CH ₂ Ph
IIIa-75	H	CH ₃	Ph	thiazol-2-yl
IIIa-76	H	CH ₃	cyclohexyl	piperidin-1-yl

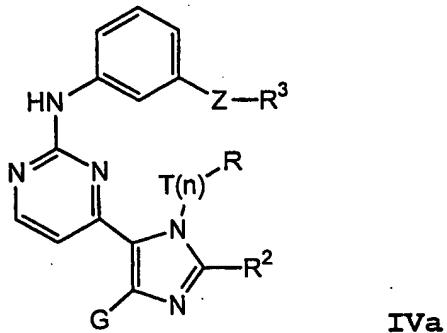
No.	G	-T _(n) -R	R ¹	R ²
IIIa-77	H	CH ₃	cyclohexyl	4-CONHMe-phenyl
IIIa-78	H	CH ₂ OCH ₃	H	4-CO ₂ H-phenyl
IIIa-79	H	CH ₂ OCH ₃	H	4-Cl-phenyl
IIIa-80	H	CH ₂ OCH ₃	H	4-CF ₃ -phenyl
IIIa-81	H	CH ₂ OCH ₃	H	4-CH ₃ -phenyl
IIIa-82	H	CH ₂ OCH ₃	H	2-Cl-phenyl
IIIa-83	H	CH ₂ OCH ₃	H	4-OCH ₃ -phenyl
IIIa-84	H	CH ₂ OCH ₃	H	4-CF ₃ -phenyl
IIIa-85	H	CH ₂ OCH ₃	H	2-Cl-phenyl
IIIa-86	H	CH ₂ OCH ₃	H	4-OCH ₃ -phenyl
IIIa-87	H	CH ₂ OCH ₃	Ph	4-Cl-phenyl
IIIa-88	H	CH ₂ OCH ₃	Ph	4-Cl-phenyl
IIIa-89	H	CH ₂ OCH ₃	Ph	4-CF ₃ -phenyl
IIIa-90	H	CH ₂ OCH ₃	Ph	4-CF ₃ -phenyl
IIIa-91	H	CH ₂ OCH ₃	Ph	4-CH ₃ -phenyl
IIIa-92	H	CH ₂ OCH ₃	Ph	4-CH ₃ -phenyl
IIIa-93	H	CH ₂ OCH ₃	CH ₂ Ph	pyridin-3-yl
IIIa-94	H	CH ₂ OCH ₃	COPh	CONHCH ₂ Ph
IIIa-95	H	CH ₂ OCH ₃	SO ₂ Me	CH ₂ Ph
IIIa-96	H	CH ₂ OCH ₃	Ph	thiazol-2-yl
IIIa-97	H	CH ₂ OCH ₃	cyclohexyl	piperidin-1-yl
IIIa-98	H	CH ₂ OCH ₃	cyclohexyl	4-CONHMe-phenyl
IIIb-1	H	--	4-Cl-phenyl	Ph
IIIb-2	H	--	4-F-phenyl	Ph
IIIb-3	H	--	3-OMe-Ph	Ph
IIIb-4	H	--	3,5-(OMe) ₂ -Ph	Ph
IIIb-5	H	--	Ph	Ph
IIIb-6	H	--	3-BnO-Ph	Ph
IIIb-7	H	--	4-NO ₂ -Ph	Ph
IIIb-8	H	--	3-Br-Ph	Ph
IIIb-9	H	--	3-CO ₂ CH ₃ -Ph	Ph

No.	G	-T _(n) -R	R ¹	R ²
IIIb-10	H	--	cyclohexyl	Ph
IIIb-11	H	--	4-Cl-phenyl	2-OBn-Ph
IIIb-12	H	--	3-NO ₂ -Ph	2-OBn-Ph
IIIb-13	H	--	CH ₂ -phenyl	2-OBn-Ph
IIIb-14	H	--	cyclohexyl	2-OBn-Ph
IIIb-15	H	--	3-OMe-Ph	2-OBn-Ph
IIIb-16	H	--	3,5-(OMe) ₂ -Ph	2-OBn-Ph
IIIb-17	H	--	4-Cl-phenyl	cyclohexyl
IIIb-18	H	--	3-Cl-phenyl	Ph
IIIb-19	H	--	H	4-CO ₂ H-phenyl
IIIb-20	H	--	H	4-Cl-phenyl
IIIb-21	H	--	H	4-CF ₃ -phenyl
IIIb-22	H	--	H	4-CH ₃ -phenyl
IIIb-23	H	--	H	2-Cl-phenyl
IIIb-24	H	--	H	4-OCH ₃ -phenyl
IIIb-25	H	--	H	4-CF ₃ -phenyl
IIIb-26	H	--	H	2-Cl-phenyl
IIIb-27	H	--	H	4-OCH ₃ -phenyl
IIIb-28	H	--	Ph	4-Cl-phenyl
IIIb-29	H	--	Ph	4-Cl-phenyl
IIIb-30	H	--	Ph	4-CF ₃ -phenyl
IIIb-31	H	--	Ph	4-CF ₃ -phenyl
IIIb-32	H	--	Ph	4-CH ₃ -phenyl
IIIb-33	H	--	Ph	4-CH ₃ -phenyl
IIIb-34	H	--	CH ₂ Ph	pyridin-3-yl
IIIb-35	H	--	COPh	CONHCH ₂ Ph
IIIb-36	H	--	SO ₂ Me	CH ₂ Ph
IIIb-37	H	--	Ph	thiazol-2-yl
IIIb-38	H	--	cyclohexyl	piperidin-1-yl
IIIb-39	H	--	cyclohexyl	4-CONHMe-phenyl
IIIc-1	H	--	4-Cl-phenyl	Ph

No.	G	-T _(n) -R	R ¹	R ²
IIIC-2	H	--	4-F-phenyl	Ph
IIIC-3	H	--	3-OMe-Ph	Ph
IIIC-4	H	--	3,5-(OMe) ₂ -Ph	Ph
IIIC-5	H	--	Ph	Ph
IIIC-6	H	--	3-BnO-Ph	Ph
IIIC-7	H	--	4-NO ₂ -Ph	Ph
IIIC-8	H	--	3-Br-Ph	Ph
IIIC-9	H	--	3-CO ₂ CH ₃ -Ph	Ph
IIIC-10	H	--	cyclohexyl	Ph
IIIC-11	H	--	4-Cl-phenyl	2-OBn-Ph
IIIC-12	H	--	3-NO ₂ -Ph	2-OBn-Ph
IIIC-13	H	--	CH ₂ -phenyl	2-OBn-Ph
IIIC-14	H	--	cyclohexyl	2-OBn-Ph
IIIC-15	H	--	3-OMe-Ph	2-OBn-Ph
IIIC-16	H	--	3,5-(OMe) ₂ -Ph	2-OBn-Ph
IIIC-17	H	--	4-Cl-phenyl	cyclohexyl
IIIC-18	H	--	3-Cl-phenyl	Ph
IIIC-19	H	--	H	4-CO ₂ H-phenyl
IIIC-20	H	--	H	4-Cl-phenyl
IIIC-21	H	--	H	4-CF ₃ -phenyl
IIIC-22	H	--	H	4-CH ₃ -phenyl
IIIC-23	H	--	H	2-Cl-phenyl
IIIC-24	H	--	H	4-OCH ₃ -phenyl
IIIC-25	H	--	H	4-CF ₃ -phenyl
IIIC-26	H	--	H	2-Cl-phenyl
IIIC-27	H	--	H	4-OCH ₃ -phenyl
IIIC-28	H	--	Ph	4-Cl-phenyl
IIIC-29	H	--	Ph	4-Cl-phenyl
IIIC-30	H	--	Ph	4-CF ₃ -phenyl
IIIC-31	H	--	Ph	4-CF ₃ -phenyl
IIIC-32	H	--	Ph	4-CH ₃ -phenyl

No.	G	-T _(n) -R	R ¹	R ²
IIIc-33	H	--	Ph	4-CH ₃ -phenyl
IIIc-34	H	--	CH ₂ Ph	pyridin-3-yl
IIIc-35	H	--	COPh	CONHCH ₂ Ph
IIIc-36	H	--	SO ₂ Me	CH ₂ Ph
IIIc-37	H	--	Ph	thiazol-2-yl
IIIc-38	H	--	cyclohexyl	piperidin-1-yl
IIIc-39	H	--	cyclohexyl	4-CONHMe-phenyl

[0086] A more preferred embodiment relates to compounds of formula IVa:



5 or a pharmaceutically acceptable derivative thereof, wherein R², R³, n, T, R, and G are as defined above.

[0087] Preferred R², R³, n, T, R and G groups of formula IVa are those described above for formula IIa.

[0088] Preferred -Z-R³ groups of the Ar¹ group of formula I are those wherein Z is a C₁₋₄ alkylidene chain wherein one methylene unit of Z is optionally replaced by -O-, -NH-, -NHC(O)-, -NHC(O)O-, -NHSO₂-, -C(O)NH-, or wherein R³ is selected from -N(R)₂, -NHC(O)R, or Ar³ wherein Ar³ is a 5-6 membered heterocyclic or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen, or sulfur. The Ar³ group is optionally substituted with -R', -OR', -N(R')₂, or oxo. More preferred Z-R³ groups of the Ar¹ group of formula IVa are selected from -O-CH₂-phenyl, -O(CH₂)₃OH,

-O(CH₂)₃NH(CH₂)₂OH, -O(CH₂)₂NH(CH₂)₂OH,
-O(CH₂)₃N(hydroxyethyl)(methyl), -O(CH₂)₃pyrrolidin-1-yl,
-O(CH₂)₂morpholin-4-yl, -O(CH₂)₃N(Me)₂, -O(CH₂)₃N(Et)₂,
-O(CH₂)₃(4-hydroxyethyl piperazin-1-yl), -O(CH₂)₃piperazin-
5 1-yl, -O(CH₂)₃(4-hydroxymethylpiperidin-1-yl), -O(CH₂)₃(4-
hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂,
-NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-
aminothiazol-4-yl), NHCOCH₂cyclopropyl, -NHCO(CH₂)₂N(Et)₂,
-NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHC(O)-
10 pyrrolidin-1-yl, -NHCOmorpholin-4-yl,
-NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl,
-NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-
yl.

[0089] Preferred compounds of formula IVa are those
15 having one or more, more preferably more than one, and
most preferably all, of the features selected from the
group consisting of:

(a) R² is Ar² or -CH₂-Ar² wherein Ar² is selected
from 5-6 membered ring selected from carbocyclic, aryl,
20 or a heterocyclyl or heteroaryl ring having one to two
heteroatoms independently selected from nitrogen, oxygen
or sulfur, and wherein Ar² is optionally substituted by
wherein Ar² is optionally substituted with one to five
groups independently selected from -Z-R³, -R, halogen,
25 -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂,
-NRCO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R,
-SO₂R, -SO₂N(R)₂, -N(R)SO₂R, -N(R)SO₂N(R)₂, -C(O)C(O)R, or
-C(O)CH₂C(O)R;

(b) G is hydrogen;

30 (c) Z is a C₁₋₄ alkylidene chain wherein one
methylenic unit of Z is optionally replaced by -O-, -NH-,
-NHC(O)-, -NHC(O)O-, -NHSO₂-, -C(O)NH-; and

(d) R^3 is selected from $-N(R)_2$, $-NHC(O)R$, or Ar^3 wherein Ar^3 is a 5-6 membered heterocyclic or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen, or sulfur and Ar^3 is optionally substituted with $-R'$, $-OR'$, $-N(R')_2$, or oxo.

[0090] More preferred compounds of formula IVa are those having one or more, more preferably more than one, and most preferably all, of the features selected from the group consisting of:

(a) R^2 is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein each member of R^2 is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo, fluoro, trifluoromethyl, -OH, -NH₂, methyl, methoxy, or ethoxy;

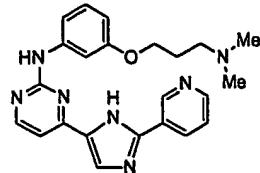
(b) G is hydrogen; and

(c) $-Z-R^3$ is selected from $-O-CH_2-phenyl$, $-O(CH_2)_3OH$, $-O(CH_2)_3NH(CH_2)_2OH$, $-O(CH_2)_2NH(CH_2)_2OH$, $-O(CH_2)_3N(hydroxyethyl)(methyl)$, $-O(CH_2)_3pyrrolidin-1-yl$, $-O(CH_2)_2morpholin-4-yl$, $-O(CH_2)_3N(Me)_2$, $-O(CH_2)_3N(Et)_2$, $-O(CH_2)_3(4-hydroxyethyl piperazin-1-yl)$, $-O(CH_2)_3piperazin-1-yl$, $-O(CH_2)_3(4-hydroxymethylpiperidin-1-yl)$, $-O(CH_2)_3(4-hydroxypiperidin-1-yl)$, $-NHCO(CH_2)_3N(Me)_2$, $-NHCO(CH_2)_3NCOCH_3$, $-NHCOCH_2pyridin-2-yl$, $-NHCOCH_2(2-aminothiazol-4-yl)$, $-NHCOCH_2cyclopropyl$, $-NHCO(CH_2)_2N(Et)_2$, $-NHCO(CH_2)_2-(piperazin-2,5-dione-3-yl)$, $-NHC(O)-pyrrolidin-1-yl$, $-NHCOMorpholin-4-yl$, $-NHCO_2CH_2tetrahydrofuran-2-yl$, $-NHCO_2tetrahydrofuran-2-yl$,

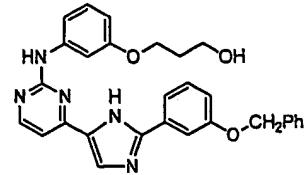
-NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl.

[0091] Exemplary structures of formula IVa are set forth in Table 6 below.

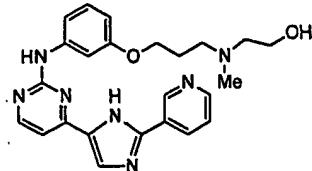
5 Table 5. Compounds of Formula IVa



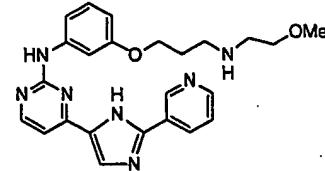
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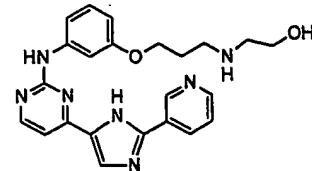
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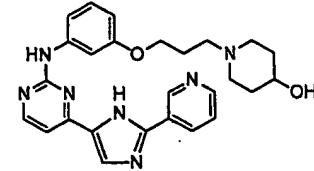
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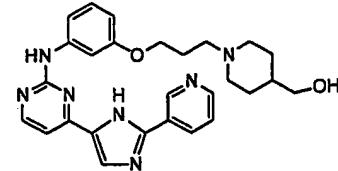
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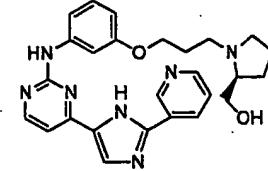
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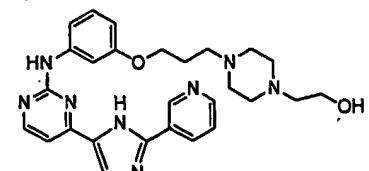
IVa-6



IVa-7



IVa-8



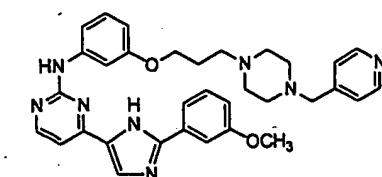
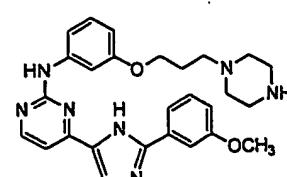
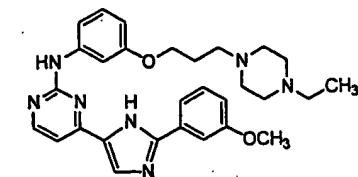
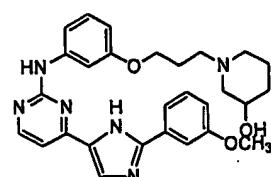
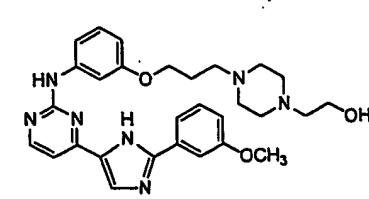
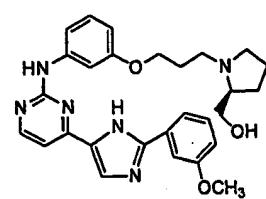
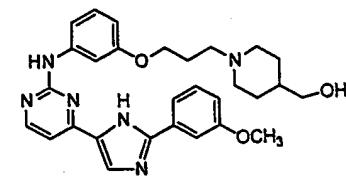
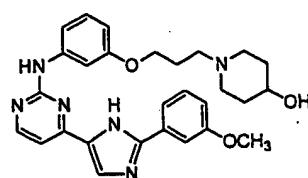
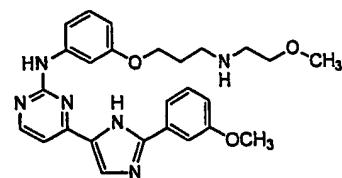
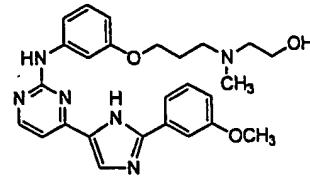
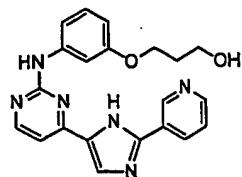
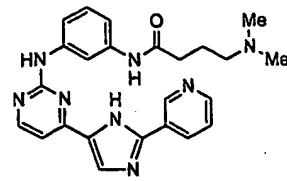
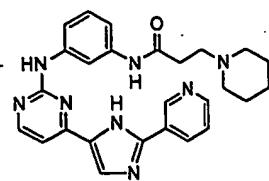
IVa-9

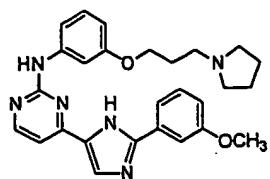


IVa-10

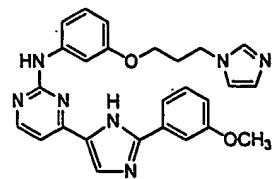
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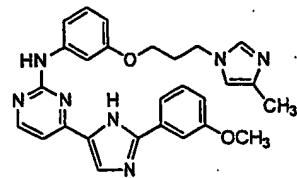




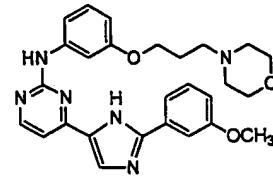
IVa-25



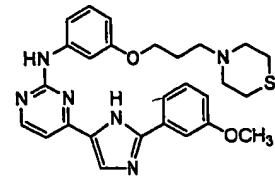
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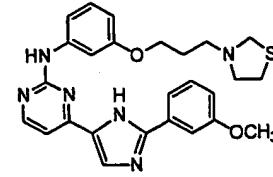
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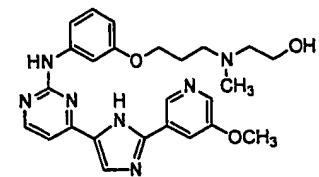
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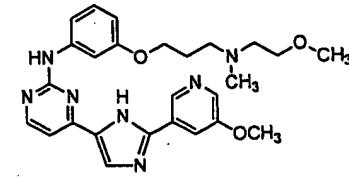
IVa-29



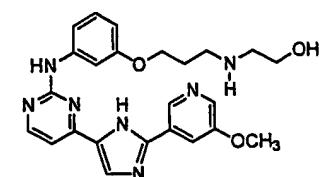
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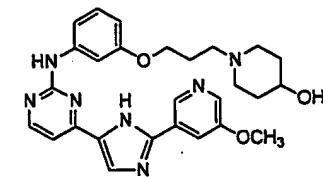
IVa-31



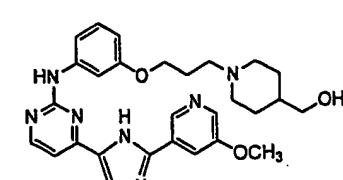
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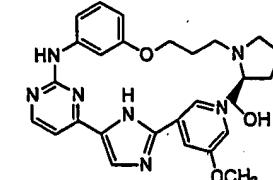
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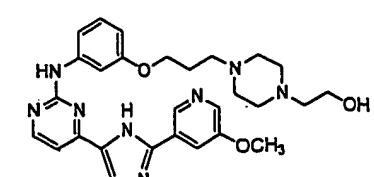
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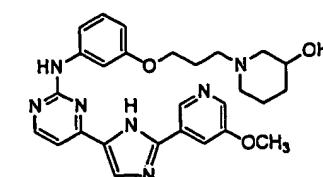
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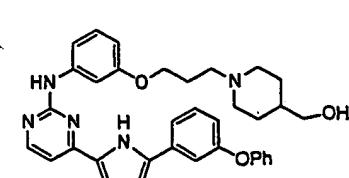
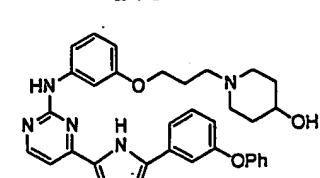
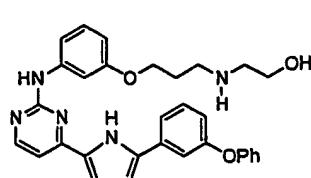
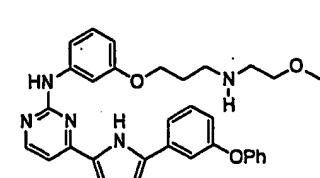
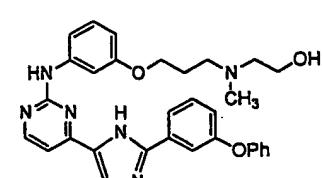
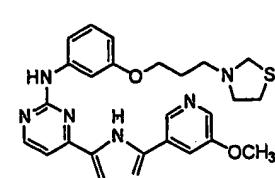
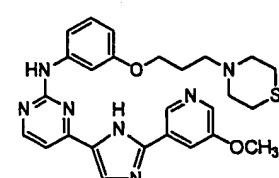
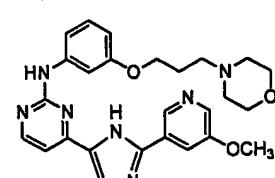
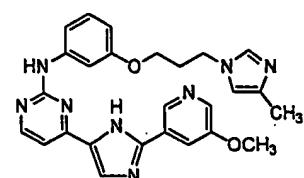
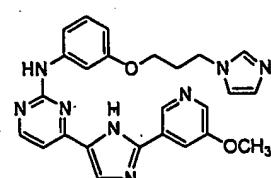
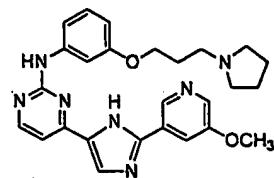
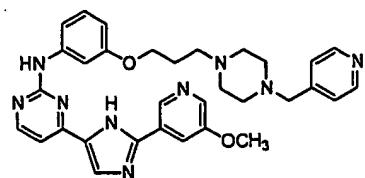
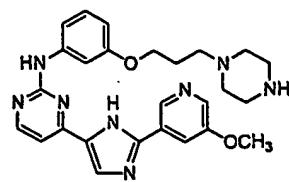
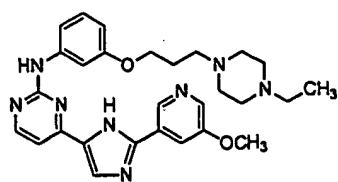
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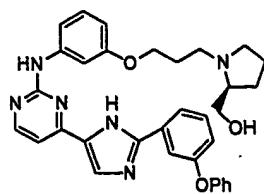


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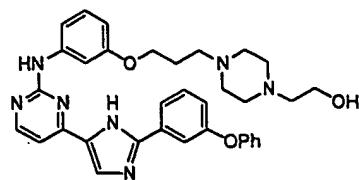


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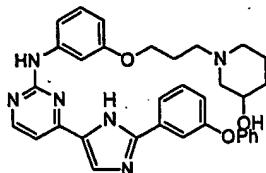




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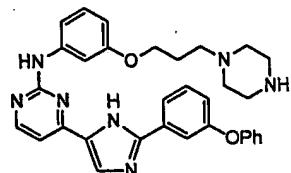
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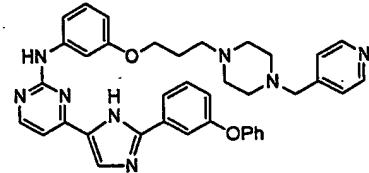
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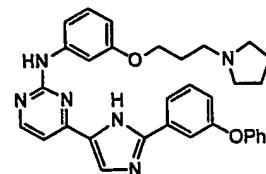
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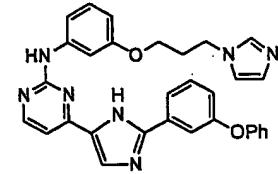
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IVa-58



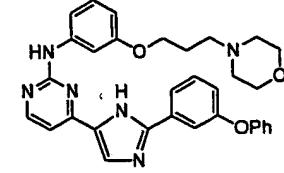
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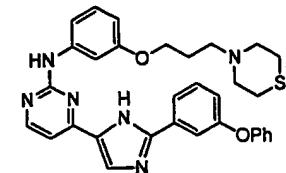
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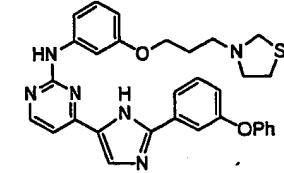
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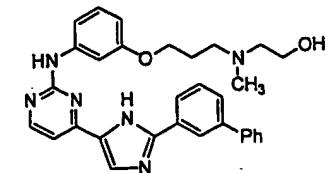
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IVa-63



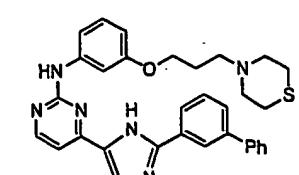
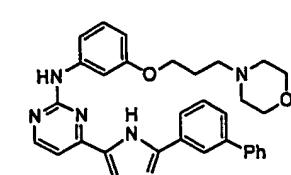
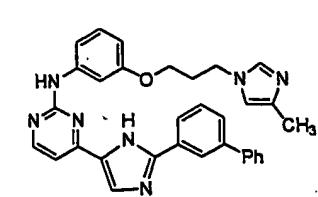
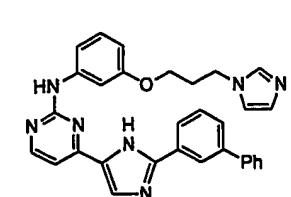
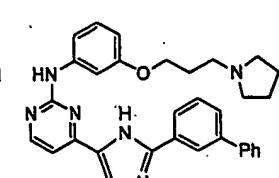
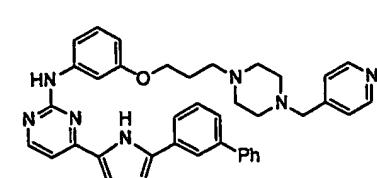
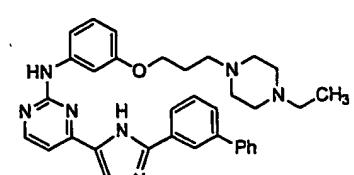
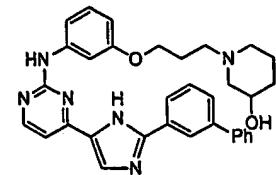
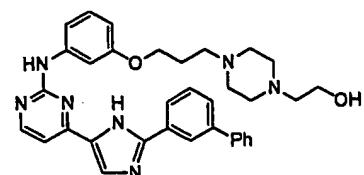
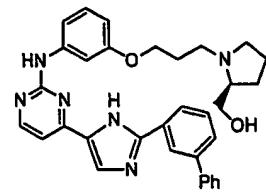
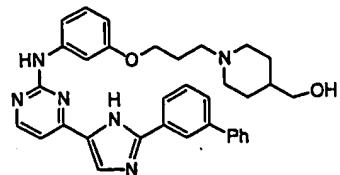
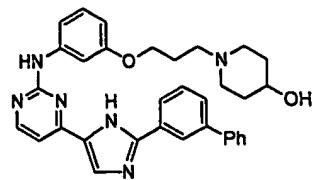
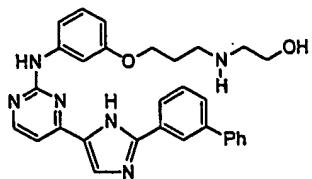
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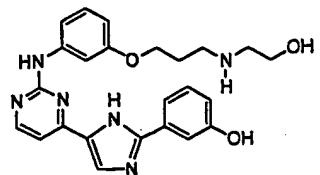
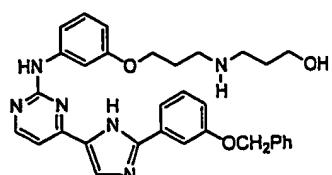
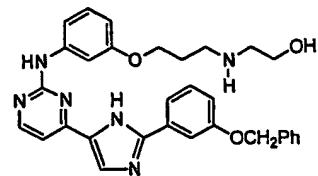
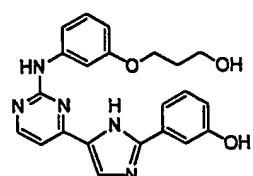
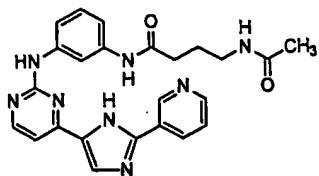
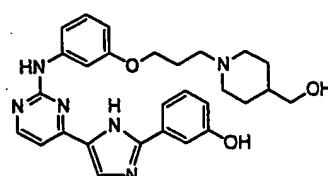
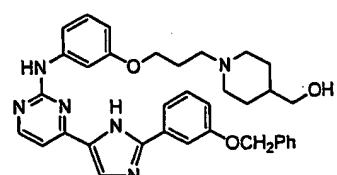
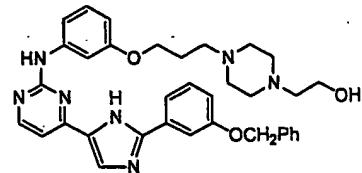
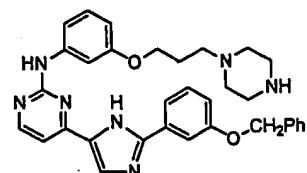
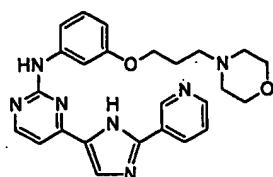
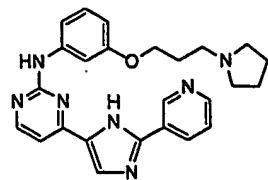
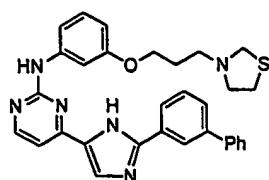


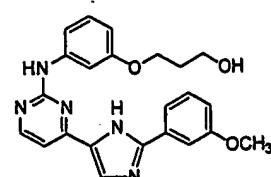
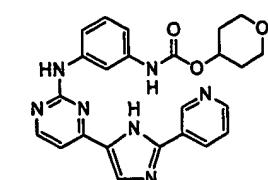
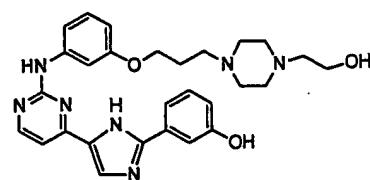
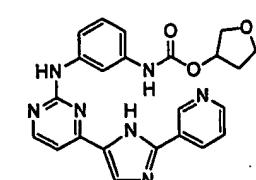
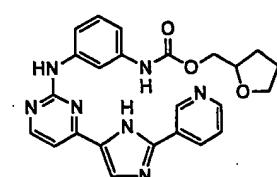
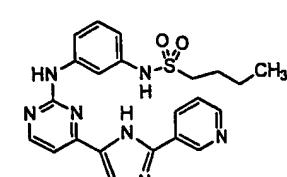
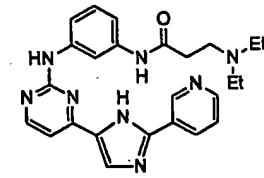
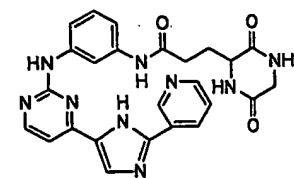
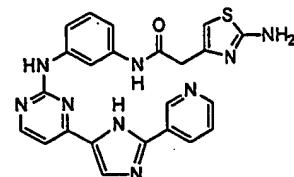
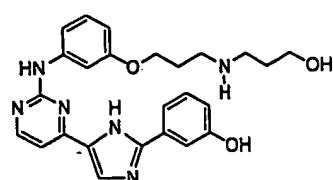
IVa-65



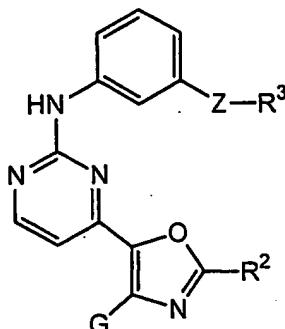
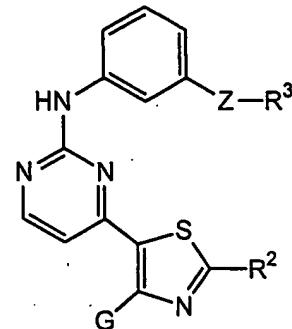
IVa-66





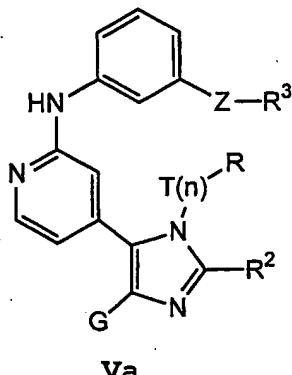
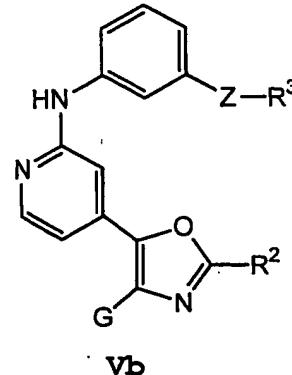
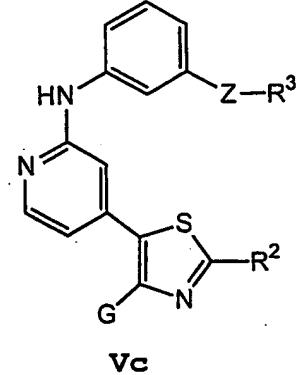


[0092] Other more preferred embodiments relate to compounds of formulae **IVb** and **IVc**:

**IVb****IVc**

5 [0093] Preferred R², -Z-R³, and G groups of the compounds of formulae **IVb** and **IVc** are as described above for the formula **IVa** compounds.

10 [0094] The formula **IV** compounds are those having a pyrimidine ring. Compounds of formula **V** having a pyridine ring are represented by the following formulae **Va**, **Vb**, and **Vc** shown below:

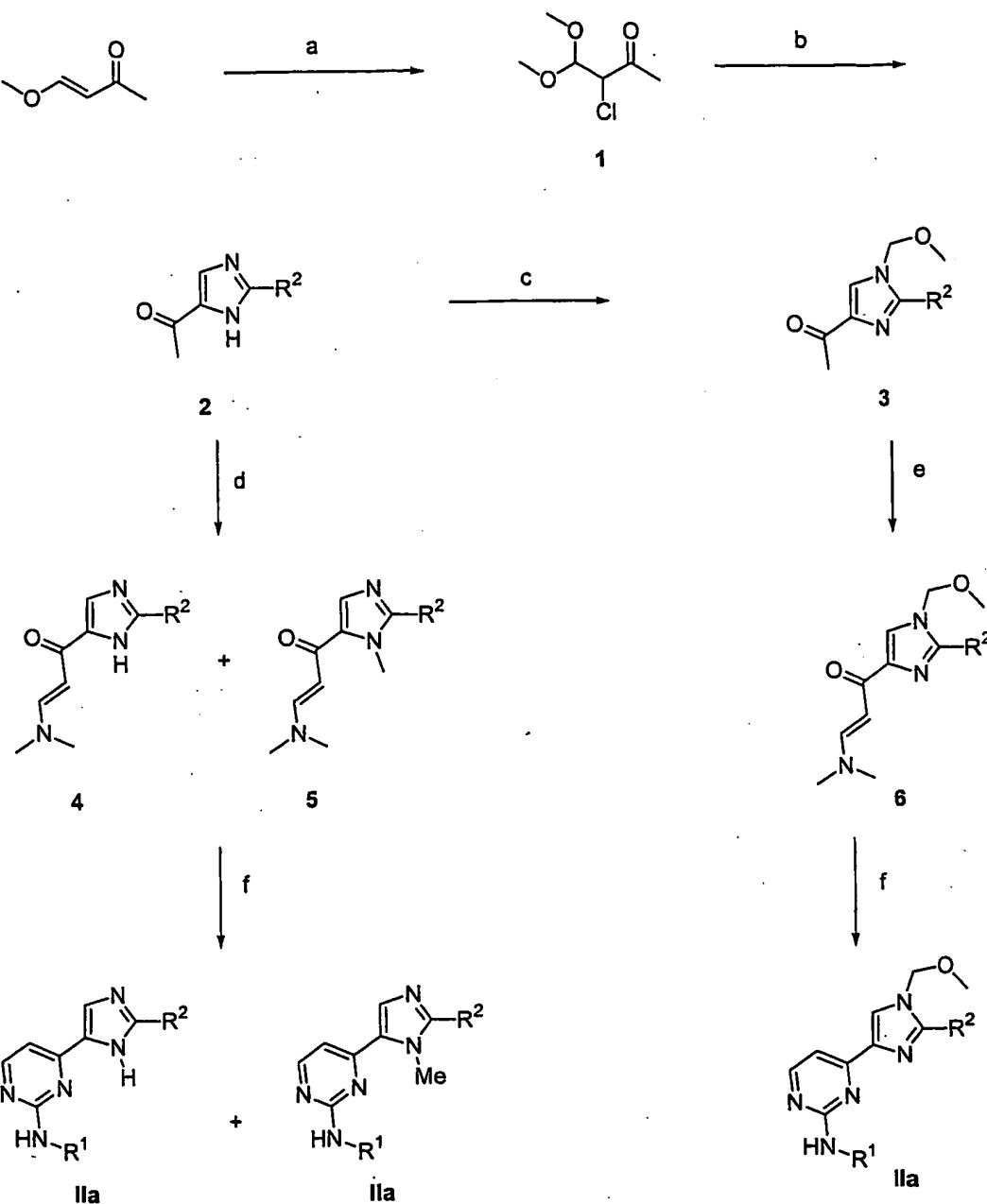
**Va****Vb****Vc**

15 [0095] The compounds of formulae **Va**, **Vb**, and **Vc** shown above are structurally similar to compounds of formulae **IVa**, **IVb**, and **IVc** where the pyrimidine ring of formulae **IVa**, **IVb**, and **IVc** is replaced by a pyridine ring. Accordingly, preferred R², -Z-R³, and G groups of the compounds of formulae **Va**, **Vb**, and **Vc** are as described above for the formulae **IVa**, **IVb**, and **IVc** compounds.

20 [0096] The present compounds may be prepared in general from known starting materials following methods

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known to those skilled in the art for analogous compounds, as illustrated by the general Schemes I and II, and the synthetic examples described herein.

Scheme I

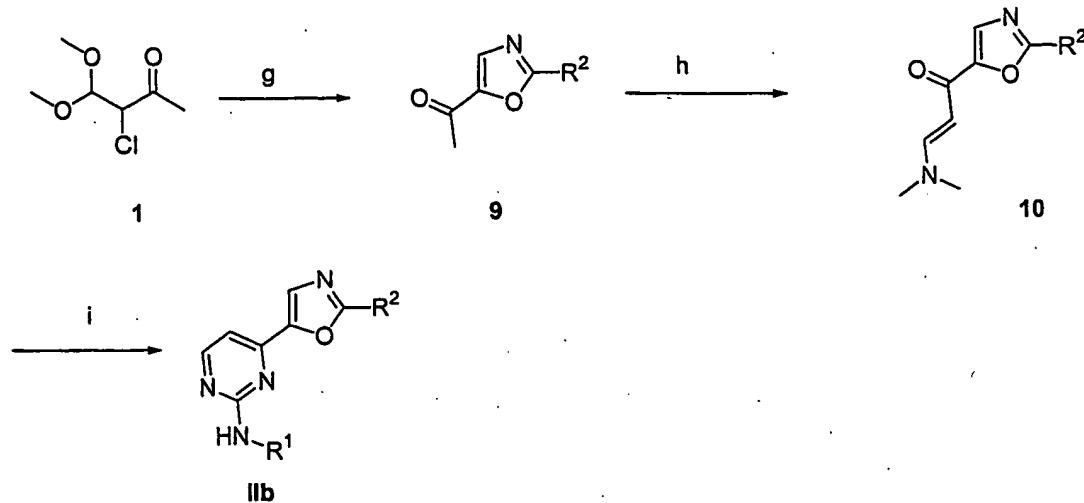
Reagents and conditions: (a) Cl_2 (gas), MeOH , pyridine, r.t.;
 (b) 1,4-dioxane, CH_3COONa , amidines, reflux;
 (c) LDA, -78°C to r.t., THF, then MOMCl ;
 (d) $(\text{CH}_3)_2\text{NCH}(\text{OCH}_3)$, toluene, 90°C ;
 (e) $(\text{CH}_3)_2\text{NCH}(\text{OCH}_3)$, CH_3CN , dimethylamine, reflux; and
 (f) MeONa , MeOH , guanidines, reflux.

[0097] Scheme I above shows a general synthetic route that is used for preparing the compounds of formula I

- 70 -

where A is $-N-T_{(n)}-R$ (formula IIa). The details of the conditions used for producing these compounds are set forth in the Examples.

Scheme II



Reagents and conditions: (g) CH_3COOH , amides, $120^\circ C$;

(h) $(CH_3)_2NCH(OCH_3)$, toluene, $90^\circ C$; and

5 (i) $MeONa$, $MeOH$, guanidines, reflux.

[0098] Scheme II above shows a general synthetic route that is used for preparing the compounds of formula I where A is oxygen (formula IIb). Scheme II can also be used to prepare compounds of formula I where A is sulfur (formula IIc) when amides in step (g) are replaced by thioamides. The details of the conditions used for producing these compounds are set forth in the Examples.

[0099] One of skill in the art may synthesize other compounds of the present invention following the teachings of the specification using reagents that are readily synthesized or commercially available.

[0100] According to another embodiment, the invention provides a method of inhibiting JNK, Src, Lck, or Aurora-2 kinase activity in a biological sample. This method comprises the step of contacting said biological sample with a compound of formula I. According to a

preferred embodiment, the invention relates to a method of inhibiting JNK, Src, Lck, or Aurora-2 kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of formula **IIa**,

5 **IIb**, **IVa**, or **IVb**.

[0101] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[0102] Inhibition of JNK, Src, Lck, or Aurora-2 kinase activity in a biological sample is useful for a variety of purposes which are known to one of skill in the art. Examples of such purposes include, but are not limited 15 to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

[0103] Compounds of formula **I** or derivatives (e.g., salts) thereof may be formulated into compositions. In a preferred embodiment, the composition is a 20 pharmaceutically acceptable composition. In one embodiment, the composition comprises an amount of a compound effective to inhibit a protein kinase, particularly JNK, Src, Lck, or Aurora-2, in a biological sample or in a patient. In another embodiment, compounds 25 of this invention and pharmaceutical compositions thereof, which comprise an amount of the compound effective to treat or prevent an JNK, Src, Lck, or Aurora-2 -mediated condition and a pharmaceutically acceptable carrier, adjuvant, or vehicle, may be 30 formulated for administration to a patient.

[0104] The amount effective to inhibit protein kinase, for example, JNK, Src, Lck, or Aurora-2, is one that measurably inhibits the kinase activity where compared to

the activity of the enzyme in the absence of an inhibitor. "Measurable inhibition" means a measurable change in activity between a sample containing said inhibitor and a sample containing said protein kinase only. Any method may be used to determine inhibition, such as, for example, the biological testing examples described below.

[0105] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.

[0106] The term "patient" includes human and veterinary subjects.

[0107] Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0108] The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally

or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

5 Preferably, the compositions are administered orally, intraperitoneally or intravenously.

[0109] Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension.

10 These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed

15 as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-

20 acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents which are commonly

25 used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers

which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

5 [0110] The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used
10 include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active
15 ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[0111] Alternatively, the pharmaceutical compositions of this invention may be administered in the form of
20 suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials
25 include cocoa butter, beeswax and polyethylene glycols.

[0112] The pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including
30 diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0113] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

5 [0114] For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention
10 include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or
15 cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol,
20 benzyl alcohol and water.

[0115] For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

[0116] The pharmaceutical compositions of this
30 invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline,

employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

5 [0117] According to a preferred embodiment, the pharmaceutical compositions of this invention are orally administered.

10 [0118] According to another embodiment, the present invention relates to a pharmaceutically acceptable derivative of a compound of formula I. In a preferred embodiment, said pharmaceutically acceptable derivative is of a compound of formula IIa, IIb, IVa, or IVb.

15 [0119] In addition to the compounds of this invention, pharmaceutically acceptable derivatives of the compounds of this invention may also be employed in compositions to treat or prevent the diseases or disorders identified herein.

20 [0120] A "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, salt of an ester or other derivative of a compound of this invention which, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof. The methods for preparing salts or esters of a compound of this invention are known to one of skill in the art. Particularly favored derivatives are those that increase the bioavailability of the compounds of this invention when such compounds are administered to a patient (e.g., by allowing an 25 orally administered compound to be more readily absorbed into the blood) or which enhance delivery of the parent compound to a biological compartment (e.g., the brain or lymphatic system) relative to the parent species.

[0121] Pharmaceutically acceptable derivatives of the compounds of this invention include, without limitation, esters, amino acid esters, phosphate esters, metal salts and sulfonate esters.

5 [0122] Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include acetate, adipate, alginate, aspartate, benzoate, 10 benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hydrochloride, 15 hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, salicylate, 20 succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their 25 pharmaceutically acceptable acid addition salts.

[0123] Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ salts. This invention also envisions the quaternization 30 of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

[0124] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The dosage of compound will also depend upon which particular compound is in the composition.

[0125] The compounds of this invention are inhibitors of JNK, Src, Lck, or Aurora-2 kinase as determined by enzymatic assay. Accordingly, these compounds are useful for treating JNK-, Src-, Lck-, or Aurora-2-mediated diseases or conditions.

[0126] Another aspect of this invention relates to a method for treating a JNK-, Src-, Lck-, or Aurora-2-mediated disease in a patient, which method comprises administering to a patient in need thereof, a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable composition comprising said compound. According to a preferred embodiment, the invention relates to administering a compound of formula Ia, IIa, IIb, IIc, IIIa, IIIb, IIIc, IVa, IVb, IVc, Va, Vb, or Vc, or a pharmaceutically acceptable composition comprising said compound. A more preferred embodiment relates to administering a compound of formula IIa, IIb, IVa, or IVb, or a pharmaceutically acceptable composition comprising said compound.

[0127] Yet another aspect of this invention relates to a method for lessening the severity of a JNK-, Src-, Lck-, or Aurora-2-mediated disease in a patient, which method comprises administering to a patient in need

thereof, a therapeutically effective amount of a compound of formula I, or a pharmaceutically acceptable composition comprising said compound. According to a preferred embodiment, the invention relates to

- 5 administering a compound of formula Ia, IIa, IIb, IIc,
IIIa, IIIb, IIIc, IVa, IVb, IVc, Va, Vb, or Vc, or a pharmaceutically acceptable composition comprising said compound. A more preferred embodiment relates to administering a compound of formula IIa, IIb, IVa, or
10 IVb, or a pharmaceutically acceptable composition comprising said compound.

[0128] The activity of the compounds of this invention as kinase inhibitors may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the kinase activity or ATPase activity of activated enzyme, for example JNK, Lck, Src or Aurora-2. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to JNK, Lck, Src, or Aurora-2 and may be measured either by radiolabelling the inhibitor prior to binding, isolating the inhibitor/JNK, inhibitor/Lck, or inhibitor/Src complex and determining the amount of radiolabel bound, or by running a competition experiment where new compounds are incubated with JNK, Lck, Src, or Aurora-2 bound to known radioligands. One may use any type or isoform of JNK, Lck, Src, or Aurora-2, depending upon which JNK, Lck, Src, or Aurora-2 type or isoform is to be inhibited. The details of the conditions used for the enzymatic assays are set forth in the Examples hereinbelow.

[0129] The term "JNK-mediated disease", "disorder", or "condition", as used herein means any disease, disorder or other deleterious condition in which JNK is known to

play a role. Such conditions, diseases or disorders include, without limitation, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, cancer, infectious diseases, 5 neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation, and conditions associated with prostaglandin endoperoxidase 10 synthase-2.

[0130] Inflammatory diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, acute pancreatitis, chronic pancreatitis, asthma, allergies, and adult respiratory 15 distress syndrome.

[0131] Autoimmune diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, 20 chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, 25 ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

[0132] Destructive bone disorders which may be treated or prevented by the compounds of this invention include, but are not limited to, osteoporosis, osteoarthritis and 30 multiple myeloma-related bone disorder.

[0133] Proliferative diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, acute myelogenous leukemia, chronic

myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma and HTLV-1 mediated tumorigenesis.

[0134] Angiogenic disorders which may be treated or prevented by the compounds of this invention include solid tumors, ocular neovasculization, infantile haemangiomas. Infectious diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, sepsis, septic shock, and Shigellosis.

[0135] Viral diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

[0136] Neurodegenerative diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), epilepsy, seizures, Huntington's disease, traumatic brain injury, ischemic and hemorrhaging stroke, cerebral ischemias or neurodegenerative disease, including apoptosis-driven neurodegenerative disease caused by traumatic injury, acute hypoxia, ischemia or glutamate neurotoxicity.

[0137] "JNK-mediated disease", "disorder" or "condition" also includes ischemia/reperfusion in stroke, heart attacks, myocardial ischemia, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, hepatic ischemia, liver disease, congestive heart failure, pathologic immune responses such as that caused by T cell activation and thrombin-induced platelet aggregation.

[0138] In addition, JNK inhibitors of the present invention may be capable of inhibiting the expression of

inducible pro-inflammatory proteins. Therefore, other "JNK-mediated diseases", "disorder" or "conditions" which may be treated by the compounds of this invention include edema, analgesia, fever and pain such as neuromuscular 5 pain, headache, cancer pain, dental pain and arthritis pain.

[0139] The compounds of this invention are also useful as inhibitors of Src-family kinases, especially Src. For a general review of these kinases see Thomas and Brugge, 10 Annu. Rev. Cell Dev. Biol. 13:513 (1997); Lawrence and Niu, Pharmacol. Ther. 77:81 (1998); and Tatosyan and Mizenina, Biochemistry (Moscow) 65:49 (2000).

Accordingly, these compounds are useful for treating Src-mediated diseases, disorders or conditions.

[0140] The term "Src-mediated disease", "disorder" or "condition" as used herein means any disease, disorder or other deleterious condition that is known to be affected by the activity of one or more Src-family kinases. Such diseases, disorders or conditions include hypercalcemia, 15 restenosis, hypercalcemia, osteoporosis, osteoarthritis, symptomatic treatment of bone metastasis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, Hashimoto's thyroiditis, Guillain-Barre syndrome, chronic obstructive pulmonary disorder, contact dermatitis, cancer, Paget's disease, asthma, ischemic or reperfusion injury, allergic disease, atopic dermatitis, and allergic rhinitis. 20 Diseases that are affected by Src activity, in particular, include hypercalcemia, osteoporosis, 25 osteoarthritis, cancer, symptomatic treatment of bone metastasis, and Paget's disease.

[0141] The term "Lck-mediated disease", "disorder" or "condition" as used herein means any disease, disorder or other deleterious condition that is known to be affected by the activity of Lck kinase. Such diseases, disorders or conditions include autoimmune diseases, allergies, rheumatoid arthritis, and leukemia.

[0142] The term "Aurora-mediated disease", "disorder", or "condition" as used herein, means any disease or other deleterious condition or disease in which an Aurora family protein kinase is known to play a role. Such diseases or conditions include, without limitation, melanoma, leukemia, or a cancer selected from colon, breast, gastric, ovarian, cervical, melanoma, renal, prostate, lymphoma, neuroblastoma, pancreatic, leukemia and bladder.

[0143] A preferred embodiment relates to the method used to treat or prevent a JNK-mediated disease selected from inflammatory diseases, autoimmune diseases, destructive bone disorders, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, or thrombin-induced platelet aggregation.

[0144] Another preferred embodiment relates to the method used to treat or prevent a Src-mediated disease selected from hypercalcemia, osteoperosis, osteoarthritis, or symptomatic treatment of bone metastasis.

[0145] Another preferred embodiment relates to the method used to treat or prevent a Lck-mediated disease selected from autoimmune diseases, rheumatoid arthritis, or leukemia.

[0146] Another preferred embodiment relates to the method used to treat or prevent an Aurora-mediated disease selected from melanoma, leukemia, or a cancer selected from colon, breast, gastric, ovarian, cervical, 5 melanoma, renal, prostate, lymphoma, neuroblastoma, pancreatic, leukemia and bladder

[0147] Depending upon the particular protein kinase-mediated condition to be treated or prevented, additional therapeutic agents, which are normally administered to 10 treat or prevent that condition, may be administered together with the compounds of this invention. For example, in the treatment of cancer, other chemotherapeutic or anti-proliferative agents may be combined with the compounds of this invention to treat 15 cancer. These agents include, without limitation, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

[0148] Other examples of agents the compounds of this 20 invention may also be combined with include, without limitation, anti-diabetic agents including insulin or insulin analogues in injectable or inhalation form, glitazones, alpha glucosidase inhibitors, biguanides, insulin sensitizers, and sulfonyl ureas; anti- 25 inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, 30 cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-

- Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids,
- 5 cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.
- 10 [0149] Those additional agents may be administered separately from the compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with the compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.
- 15 [0150] The amount of both, the compound and the additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, the compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of a compound of formula I can be administered.
- 20 [0151] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional

therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 - 100 µg/kg body weight/day of the

5 additional therapeutic agent can be administered.

[0152] The compounds of this invention, or pharmaceutical compositions thereof, may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves,

10 vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk

clot formation or platelet activation. These unwanted

15 effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Suitable coatings and the general preparation of coated implantable devices are described in United States Patents 6,099,562; 5,886,026;

20 and 5,304,121, the contents of which are incorporated herein by reference. The coatings are typically

biocompatible polymeric materials such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl

25 acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, phospholipids or combinations thereof to impart controlled release characteristics in the composition.

30 Implantable devices coated with a compound of this invention are another embodiment of the present invention.

[0153] Each of the aforementioned methods directed to the inhibition of JNK, Lck, Src, or Aurora-2, or the treatment of a disease alleviated thereby, is preferably carried out with a preferred compound of formula I, IIa, 5 IIb, IVa, or IVb, as described above. More preferably, each of the aforementioned methods is carried out with a preferred compound of formula IIa, IIb, IVa, or IVb.

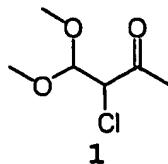
[0154] In order that the invention described herein may be more fully understood, the following examples are 10 set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXAMPLES

15 [0155] As used herein, the term "R_t(min)" refers to the HPLC retention time, in minutes, associated with the compound using the HPLC method specified. Unless otherwise indicated, the HPLC methods utilized to obtain the reported retention times are as follows:

20 Method-A: Column: YMC ODS-AQ, 2 x 50 mm
Gradient: 10% → 90% CH₃CN/water (0.1% TFA)
over 5 minutes; 90% CH₃CN/water (0.1% TFA)
for 0.7 minutes; 90% → 10% CH₃CN/water
(0.1% TFA) over 0.1 minutes; and then 10%
CH₃CN/water (0.1% TFA) for 1.2 minutes
25 Flow rate: 1 mL/minute;

Method-B: Column: YMC C18, 3 x 150 mm
Gradient: 10% → 90% CH₃CN/water (0.1% TFA)
over 7 minutes; 90% CH₃CN/water (0.1% TFA)
for 2.0 minutes; 90% → 10% CH₃CN/water
(0.1% TFA) over 1.0 minutes; and then 10%
CH₃CN/water (0.1% TFA) for 2.0 minutes
30 Flow rate: 1 mL/minute.

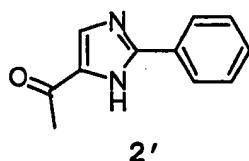
Example 1

1

3-Chloro-4,4-dimethoxybutan-2-one (1):

[0156] To a solution of 4-methoxy-but-3-en-2-one (9.0 g, 90.0 mmol) in 100 ml MeOH was added pyridine (14.2 g, 180 mmol). Gaseous Cl₂ was introduced into the above mixture under vigorous stirring at room temperature. After 5 minutes, Cl₂ source was removed and the reaction was cooled to room temperature. The resultant reaction mixture was concentrated to yellow oil under vacuo. and was then partitioned between CH₂Cl₂ and aqueous NaHCO₃. The aqueous layer was extracted with CH₂Cl₂ (150 ml x 3), and the combined organic layers were dried over Na₂SO₄. Removal of the solvent afforded a crude material in which desired product (1) was the major product. The resulting crude material was used without further purification. ¹H NMR (CDCl₃, ppm) δ: 4.45(d, 1H), 4.12(d, 1H), 3.25(s, 3H), 3.22(s, 3H) and 2.20(s, 3H).

20

Example 2

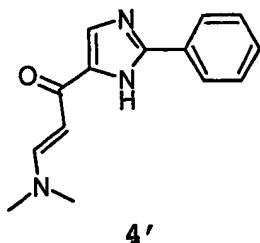
2'

1-(2-Phenyl-3-H-imidazol-4-yl)-ethanone (2'):

[0157] To a solution of 1 (2.2 g, 13.3 mmol) in 20 ml 1,4-dioxane was added benzimidine (3.24 g, 20.0 mmol) and sodium acetate (2.83 g, 33.3 mmol). The reaction was refluxed in an oil bath at 110 °C over 60 hours. After the reaction was cooled to room temperature, the salt was

removed through a plug of celite and the filtrate was concentrated to a red oil. This oil was then taken up in ethyl acetate (50 ml) and extracted with 1N HCl (17 ml x 3). The combined aqueous layers were basified with 5 aqueous Na₂CO₃ and then were extracted with ethyl acetate (50 ml x3). The combined organic layers were dried over Na₂SO₄ and the solvent was removed. Purification by chromatography using CH₂Cl₂/MeOH (95:5/v:v) afforded 2' (1.02 g) as the desired product in 41% yield. ¹H NMR 10 (acetone-d₆, ppm) δ: 7.4-8.1(m, 7H) and 2.42 (s, 3H).

Example 3



3-Dimethylamino-1-(2-phenyl-3H-imidazol-4-yl)-propenone

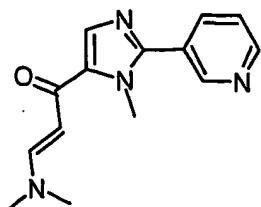
15 (4'):

[0158] To a solution of 2' (186 mg, 1.0 mmol) in 5 ml toluene was added dimethoxymethyldimethylamine (595 mg, 5.0 mmol). The reaction was heated in a sealed tube at 98 °C overnight. The reaction was cooled to room 20 temperature and was then concentrated to an oil under vacuo. Purification of the crude oil by chromatography using 3% MeOH in CH₂Cl₂ afforded the desired product 4' in 30% yield. ¹H NMR (CDCl₃, ppm) δ: 8.05 (d, 2H), 7.7 (d, 1H), 7.6 (s, 1H), 7.3 (m, 3H), 5.6 (d, 2H), 3.1 (bs, 3H) 25 and 2.8 (bs, 3H).

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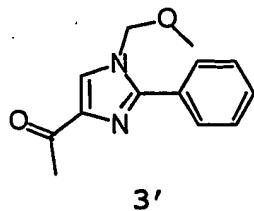
Example 4

5'



3-Dimethylamino-1-(3-methyl-2-pyridin-3-yl-3H-imidazol-4-yl)-propenone (5'):

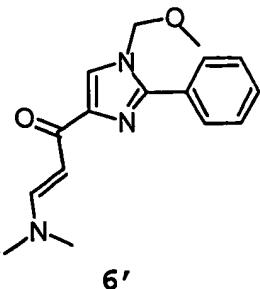
5 [0159] 1-(2-Pyridin-3-yl-3H-imidazol-4-yl)-ethanone (2.0 g, 7.4 mmol) was added to dimethoxymethyl-dimethylamine (7.15 g, 60.0 mmol). The mixture was heated at 75 °C for 2 hours in a sealed tube. The reaction mixture was cooled to room temperature and was 10 then concentrated to an oil under *vacuo*. Purification of the crude oil by chromatography using 5% MeOH in CH₂Cl₂ afforded desired product 5' (832 mg) in 43.9% yield. ¹H NMR (CD₃OD, ppm) δ: 8.85 (s, 1H), 8.70 (d, 1H), 8.16 (d, 1H), 7.80 (s, 1H), 7.75 (d, 1H), 7.62 (dd, 1H), 5.75 (d, 1H), 3.98 (s, 3H), 3.23 (bs, 3H) and 2.96 (bs, 3H).

Example 5

3'

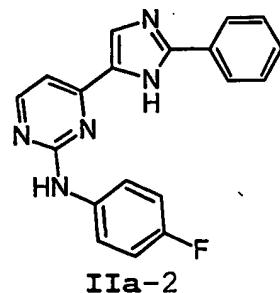
1-(1-Methoxymethyl-2-phenyl-1H-imidazol-4-yl)ethanone**(3'):**

5 [0160] To a solution of **2'** (696 mg, 3.74 mmol) in 30 ml anhydrous THF was added lithium bis(trimethylsilyl)-amide (1M in THF, 3.74 ml, 3.74 mmol) at -78 °C. After 10 minutes, the reaction mixture was warmed to room temperature and maintained at this temperature for 10 minutes and then was cooled to -78 °C again. MOMCl (284 uL, 3.74 mmol) was added to the reaction mixture. The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was then poured into aqueous NaHCO₃ and extracted with ethyl acetate (50 ml x 3). The combined organic layers were dried over anhydrous Na₂SO₄. The solvent was removed and the crude material was purified by chromatography using 2% MeOH in CH₂Cl₂ to afford 630 mg of **3'** as the desired product in 73.6% yield. ¹H NMR (CDCl₃, ppm) δ: 7.88 (s, 1H), 7.75 (m, 2H), 7.45 (m, 3H), 5.25 (s, 2H), 3.38 (s, 3H) and 2.55 (s, 3H).

Example 6

3-Dimethylamino-1-(1-methoxymethyl-2-phenyl-1H-imidazol-4-yl)-propenone (6'):

5 [0161] To a solution of 3' (630 mg, 2.73 mmol) in 5 ml CH₃CN was added dimethoxymethyldimethyl-amine (586 mg, 4.93 mmol) and dimethylamine in THF (0.5 M, 1.4 ml, 0.7 mmol). The reaction was refluxed in a sealed tube for 48 hours. The reaction was cooled to room temperature and 10 the solvent was removed in vacuo. The crude material was purified by chromatography using 2% MeOH in CH₂Cl₂ to afford 397 mg of 6' as the desired product in 51.2% yield. ¹H NMR (CDCl₃, ppm) δ: 7.90 (d, 1H), 7.80 (m, 3H), 7.40 (m, 3H), 6.12 (d, 1H), 5.22 (d, 2H), 3.36 (s, 3H), 15 3.20 (bs, 3H) and 2.92 (bs, 3H).

Example 7

20 **(4-Fluoro-phenyl)-[4-(2-phenyl-3H-imidazol-4-yl)-pyrimidin-2-yl]-amine (IIa-2):**

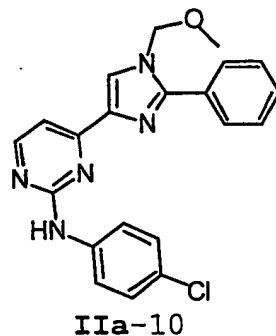
[0162] To a solution of 4' (50.0 mg, 0.21 mmol) in 4 ml anhydrous MeOH was added N-(4-fluoro-phenyl)-guanidine

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(36.8 mg, 0.24 mmol) and MeONa in MeOH (0.5M, 0.2 ml, 0.1 mmol). The reaction was refluxed in a sealed tube overnight. The crude material was subjected to preparative HPLC to afford the desired product IIa-2 in 5 56% yield. ^1H NMR (MeOH-d₄, ppm) δ : 8.50 (d, 1H), 8.30 (s, 1H), 8.02 (d, 2H), 7.70 (m, 5H), 7.32 (d, 1H) and 7.12 (m, 2H); MS (M+1): 332.2; and HPLC (method B) Rt: 6.27 minutes.

10

Example 8

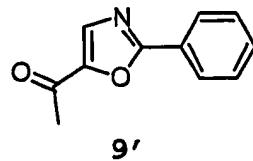


(4-Chloro-phenyl)-[4-(1-methoxymethyl-2-phenyl-1H-imidazol-4-yl)-pyrimidin-2-yl]-amine (IIa-10):

[0163] Compound IIa-10 was prepared in the same way as compound IIa-2 in 52% yield. ^1H NMR (CDCl₃, ppm) δ : 8.45 (d, 1H), 7.84 (s, 1H), 7.80 (d, 2H), 7.62 (d, 2H), 7.48 (m, 4H), 7.20 (m, 3H), 5.28 (s, 2H) and 3.42 (s, 3H); MS (M+1): 392; and HPLC (method B) Rt: 6.77 minutes.

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Example 9

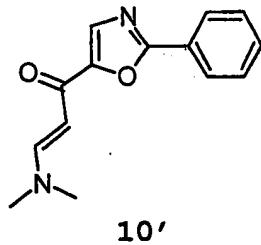


1-(2-phenyl-oxazol-5-yl)-ethanone (9'):

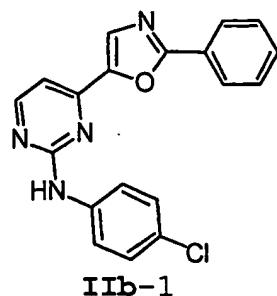
[0164] To a solution of 1 (3.32 g, 20.0 mmol) in 10 ml acetic acid was added benzamide (3.63 g, 30.0 mmol). The

reaction was heated in a sealed tube at 120 °C overnight. The reaction mixture was cooled to room temperature and poured into 100 ml water. The aqueous layer was extracted with CH₂Cl₂ (100 ml x 3) and the combined 5 organic layers were dried over Na₂SO₄. The solvent was then removed in vacuo. and the crude material was purified by chromatography using hexane:ethyl acetate (3:1/v:v) to afford 1.2 g of 9' as the desired product in 32% yield. ¹H NMR (CDCl₃, ppm) δ: 8.22 (d, 2H), 7.82 (s, 10 1H), 7.50 (m, 3H) and 2.60 (s, 3H).

Example 10



3-Dimethylamino-1-(2-phenyl-oxazol-5-yl)-propenone (10'):
[0165] To a solution of 9' (800 mg, 4.27 mmol) in 5 ml CH₃CN was added dimethoxymethyldimethylamine (916 mg, 7.70 mmol) and dimethylamine in THF (0.5M, 4.28 ml, 2.14mmol). The reaction was refluxed in a sealed tube for over 2 days. After the reaction was cooled to room temperature, 20 the solvent was removed in vacuo. The crude material was purified by chromatography using 3% MeOH in CH₂Cl₂ to afford 700 mg of 10' as the desired product in 67.7% yield. ¹H NMR (CDCl₃, ppm) δ: 8.15 (d, 2H), 7.80 (d, 1H), 7.70 (s, 1H), 7.45 (m, 3H), 5.60 (d, 1H), 3.24 (bs, 3H) 25 and 2.96 (bs, 3H).

Example 11

(4-Chloro-phenyl)-[4-(2-phenyl-oxazol-5-yl)-pyrimidin-2-yl]-amine (IIb-1):

- 5 . Compound **IIb-1** was prepared in the same manner as compound **IIa-2** in 62% yield. ^1H NMR (CDCl_3 , ppm) δ : 8.45 (d, 1H), 8.16 (d, 1H), 7.80 (s, 1H), 7.62 (d, 2H), 7.48 (m, 3H), 7.30 (d, 3H), 7.16 (s, 1H) and 7.12 (d, 1H); MS ($M+1$): 349; and HPLC (method B) Rt: 8.44 minutes.

10

Example 12

[0166] Other compounds of formula **IIa** were prepared by methods substantially similar to those described in the above Examples 7 and 8 and those illustrated in Scheme I.

- 15 The characterization data for these compounds is summarized in Table 6 below. "Y" designates ^1H NMR data was obtained and found to be consistent with the assigned structure. Compound numbers in Table 7 correspond to the compound numbers listed in Table 1.

20

Table 7. Characterization Data for Selected Compounds of Formula **IIa**

Compound No.	MS ($M+1$, obs)	Rt (min.)	Method	^1H NMR
IIa-1	348.1	2.92	A	Y
IIa-2	332.2	6.27	B	Y
IIa-3	344.2	6.35	B	Y
IIa-4	374	6.50	B	Y

IIa-5	363.2	6.35	B	Y
IIa-6	347.2	5.74	B	Y
IIa-7	329.2	5.57	B	Y
IIa-8	435.2	6.93	B	Y
IIa-9	364.2	5.69	B	Y
IIa-10	392	6.77	B	Y
IIa-11	376.1	6.50	B	Y
IIa-12	358.1	6.60	B	Y
IIa-13	403	7.01	B	Y
IIa-14	388.2	3.10	A	Y
IIa-15	418.3	3.22	A	Y
IIa-16	436.1	3.78	A	Y
IIa-17	464.3	3.98	A	Y
IIa-18	359.2	2.02	A	Y
IIa-19	389.2	2.15	A	Y
IIa-20	407.1	2.51	A	Y
IIa-21	374.2	2.35	A	Y
IIa-22	387.2	2.13	A	Y
IIa-23	430.1	7.01	B	Y
IIa-24	414.1	6.63	B	Y
IIa-25	426.1	6.61	B	Y
IIa-26	456.2	6.74	B	Y
IIa-27	474	7.11	B	Y
IIa-28	396.1	6.51	B	Y
IIa-29	502.2	7.42	B	Y
IIa-30	441.1	6.84	B	Y
IIa-31	454.1	6.76	B	Y
IIa-32	431	6.48	B	-
IIa-33	402.2	6.22	B	Y

Example 13

[0167] Other compounds of formula **IIb** were prepared by methods substantially similar to those described in the above Example 11 and those illustrated in Scheme II. The 5 characterization data for these compounds is summarized in Table 8 below. "Y" designates ^1H NMR data was obtained and found to be consistent with the assigned structure. Compound numbers in Table 8 correspond to the compound numbers listed in Table 2.

10

Table 8. Characterization Data for Selected Compounds of Formula **IIb**

Compound No.	MS (M+1, obs)	Rt (min.)	Method	^1H NMR
IIb-1	349	8.44	B	Y
IIb-2	333	7.88	B	Y
IIb-3	345	7.88	B	Y
IIb-4	375.1	7.98	B	Y
IIb-5	315	7.77	B	Y
IIb-6	421.2	8.68	B	Y
IIb-7	360.1	8.35	B	Y
IIb-8	392.9	7.22	B	Y
IIb-9	373.1	4.71	B	Y
IIb-10	321.1	5.51	B	Y
IIb-11	455.1	8.89	B	Y
IIb-12	466.2	8.82	B	Y
IIb-13	435.2	7.40	B	Y
IIb-14	427.2	7.54	B	Y
IIb-15	451.2	8.43	B	Y
IIb-16	481.2	8.40	B	Y
IIb-17	355.2	4.27	A	Y

[0168] The following examples demonstrate how the compounds of this invention may be tested as inhibitors of c-Jun-N-terminal, Src, and Lck kinases.

5

Example 14Cloning, Expression and Purification of JNK3 Protein

[0169] A BLAST search of the EST database using the published JNK3 α 1 cDNA as a query identified an EST clone (#632588) that contained the entire coding sequence for 10 human JNK3 α 1. Polymerase chain reactions (PCR) using *pfu* polymerase (Strategene) were used to introduce restriction sites into the cDNA for cloning into the pET-15B expression vector at the NcoI and BamHI sites. The protein was expressed in *E. coli*. Due to the poor 15 solubility of the expressed full-length protein (Met 1-Gln 422), an N-terminally truncated protein starting at Ser residue at position 40 (Ser 40) was produced. This truncation corresponds to Ser 2 of JNK1 and JNK2 proteins, and is preceded by a methionine (initiation) 20 and a glycine residue. The glycine residue was added in order to introduce an NcoI site for cloning into the expression vector. In addition, systematic C-terminal truncations were performed by PCR to identify a construct that give rise to diffraction-quality crystals. One such 25 construct encodes amino acid residues Ser40-Glu402 of JNK3 α 1 and is preceded by Met and Gly residues.

[0170] The construct was prepared by PCR using deoxyoligonucleotides:

30 5' GCTCTAGAGCTCCCATGGGCAGCAAAGCAAAGTTGACAA 3' (forward primer with initiation codon underlined) (SEQ ID NO:1) and 5' TAGCGGATCCTCATTCTGAATTCAATTACTTCCTTGTA 3' (reverse primer with stop codon underlined) (SEQ ID NO:2) as

primers and was confirmed by DNA sequencing. Control experiments indicated that the truncated JNK3 protein had an equivalent kinase activity towards myelin basic protein when activated with an upstream kinase MKK7 *in vitro*.

5 [0171] *E.coli* strain BL21 (DE3) (Novagen) was transformed with the JNK3 expression construct and grown at 30°C in LB supplemented with 100 µg/ml carbenicillin in shaker flasks until the cells were in log phase (OD₆₀₀ ~ 10 0.8). Isopropylthio-β-D-galactosidase (IPTG) was added to a final concentration of 0.8 mM and the cells were harvested 2 hours later by centrifugation.

10 [0172] *E. coli* cell paste containing JNK3 was resuspended in 10 volumes/g lysis buffer (50 mM HEPES, pH 15 7.2, containing 10% glycerol (v/v), 100 mM NaCl, 2 mM DTT, 0.1 mM PMSF, 2 µg/ml Pepstatin, 1µg/ml each of E-64 and Leupeptin). Cells were lysed on ice using a microfluidizer and centrifuged at 100,000 x g for 30 min at 4 °C. The 100,000 x g supernatant was diluted 1:5 20 with Buffer A (20 mM HEPES, pH 7.0, 10% glycerol (v/v), 2 mM DTT) and purified by SP-Sepharose (Pharmacia) cation-exchange chromatography (column dimensions: 2.6 x 20 cm) at 4 °C. The resin was washed with 5 column volumes of Buffer A, followed by 5 column volumes of Buffer A 25 containing 50 mM NaCl. Bound JNK3 was eluted with a 7.5 column volume linear gradient of 50-300 mM NaCl. JNK3 eluted between 150-200 mM NaCl.

Example 15

30 Activation of JNK3

[0173] Five mg of JNK3 was diluted to 0.5 mg/ml in 50 mM HEPES buffer, pH 7.5, containing 100 mM NaCl, 5 mM

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DTT, 20 mM MgCl₂ and 1 mM ATP. GST-MKK7(DD) was added at a molar ratio of 1:2.5 GST-MKK7:JNK3. After incubation for 30 minutes at 25°C, the reaction mixture was concentrated 5-fold by ultrafiltration in a Centriprep-30 (Amicon, Beverly, MA), diluted to 10 ml and an additional 1 mM ATP added. This procedure was repeated three times to remove ADP and replenish ATP. The final addition of ATP was 5 mM and the mixture incubated overnight at 4°C.

5 [0174] The activated JNK3/GST-MKK7(DD) reaction mixture was exchanged into 50 mM HEPES buffer, pH 7.5, containing 5 mM DTT and 5% glycerol (w/v) by dialysis or ultrafiltration. The reaction mixture was adjusted to 1.1 M potassium phosphate, pH 7.5, and purified by 10 hydrophobic interaction chromatography (at 25 °C) using a Rainin Hydropore column. GST-MKK7 and unactivated JNK3 do not bind under these conditions such that when a 1.1 to 0.05 M potassium phosphate gradient is developed over 15 60 minutes at a flow rate of 1 ml/minute, doubly phosphorylated JNK3 is separated from singly phosphorylated JNK. Activated JNK3 (i.e. doubly phosphorylated JNK3) was stored at -70°C at 0.25-1 mg/ml.

20

Example 16

25

JNK Inhibition Assay

[0175] Compounds were assayed for the inhibition of JNK3 by a spectrophotometric coupled-enzyme assay. In this assay, a fixed concentration of activated JNK3 (10 nM) was incubated with various concentrations of a 30 potential inhibitor dissolved in DMSO for 10 minutes at 30°C in a buffer containing 0.1 M HEPES buffer, pH 7.5, containing 10 mM MgCl₂, 2.5 mM phosphoenolpyruvate, 200 μM

NADH, 150 µg/mL pyruvate kinase, 50 µg/mL lactate dehydrogenase, and 200 µM EGF receptor peptide. The EGF receptor peptide has the sequence KRELVEPLTPSGEAPNQALLR, and is a phosphoryl acceptor in the JNK3-catalyzed kinase reaction. The reaction was initiated by the addition of 10 µM ATP and the assay plate is inserted into the spectrophotometer's assay plate compartment that was maintained at 30°C. The decrease of absorbance at 340 nm was monitored as a function of time. The rate data as a function of inhibitor concentration was fitted to competitive inhibition kinetic model to determine the K_i .

[0176] Table 9 shows the results of the activity of selected compounds of this invention in the JNK inhibition assay. The compound numbers correspond to the compound numbers in Tables 1-3. Compounds having a K_i less than 0.1 micromolar (µM) are rated "A", compounds having a K_i between 0.1 and 1 µM are rated "B" and compounds having a K_i greater than 1 µM are rated "C".

20 Table 9. JNK3 Activity of Selected Compounds

No.	Activity	No.	Activity	No.	Activity
IIa-10	C	IIa-11	C	IIa-12	C
IIa-13	C	IIa-14	C	IIa-15	C
IIa-16	C	IIa-17	C	IIa-18	B
IIa-19	B	IIa-20	B	IIa-21	B
IIa-22	B	IIa-23	B	IIa-24	B
IIa-25	A	IIa-26	B	IIa-27	B
IIa-28	B	IIa-29	B	IIa-30	B
IIa-31	B	IIa-32	B	IIa-33	A
IIb-1	C	IIb-2	B	IIb-3	B
IIb-4	B	IIb-5	B	IIb-6	B

IIb-7	B	IIb-17	C	IIc-22	A
IIc-23	B	IIc-24	C	IIc-25	C

Example 17

[0177] The compounds of this invention can be evaluated as inhibitors of human Src kinase using either 5 a radioactivity-based assay or spectrophotometric assay.

Src Inhibition Assay A: Radioactivity-based Assay

[0178] The compounds can be assayed as inhibitors of full length recombinant human Src kinase (from Upstate Biotechnology, cat. no. 14-117) expressed and purified 10 from baculo viral cells. Src kinase activity is monitored by following the incorporation of ^{33}P from ATP into the tyrosine of a random poly Glu-Tyr polymer substrate of composition, Glu:Tyr = 4:1 (Sigma, cat. no. P-0275). The following are the final concentrations of 15 the assay components: 0.05 M HEPES, pH 7.6, 10 mM MgCl₂, 2 mM DTT, 0.25 mg/ml BSA, 10 μM ATP (1-2 μCi ^{33}P -ATP per reaction), 5 mg/ml poly Glu-Tyr, and 1-2 units of recombinant human Src kinase. In a typical assay, all 20 the reaction components with the exception of ATP are pre-mixed and aliquoted into assay plate wells.

Inhibitors dissolved in DMSO are added to the wells to give a final DMSO concentration of 2.5%. The assay plate is incubated at 30°C for 10 min before initiating the reaction with ^{33}P -ATP. After 20 min of reaction, the 25 reactions are quenched with 150 μl of 10% trichloroacetic acid (TCA) containing 20 mM Na₃PO₄. The quenched samples are then transferred to a 96-well filter plate (Whatman, UNI-Filter GF/F Glass Fiber Filter, cat no. 7700-3310) installed on a filter plate vacuum manifold. Filter 30 plates are washed four times with 10% TCA containing 20

mM Na₃PO₄ and then 4 times with methanol. 200 μ l of scintillation fluid is then added to each well. The plates are sealed and the amount of radioactivity associated with the filters is quantified on a TopCount scintillation counter. The radioactivity incorporated is plotted as a function of the inhibitor concentration. The data is fitted to a competitive inhibition kinetics model to get the K_i for the compound.

Src Inhibition Assay B: Spectrophotometric Assay

10 [0179] The ADP produced from ATP by the human recombinant Src kinase-catalyzed phosphorylation of poly Glu-Tyr substrate is quantified using a coupled enzyme assay (Fox et al., Protein Sci. 7:2249(1998)]. In this assay one molecule of NADH is oxidized to NAD for every 15 molecule of ADP produced in the kinase reaction. The disappearance of NADH can be conveniently followed at 340 nm.

20 [0180] The following are the final concentrations of the assay components: 0.025 M HEPES, pH 7.6, 10 mM MgCl₂, 2 mM DTT, 0.25 mg/ml poly Glu-Tyr, and 25 nM of recombinant human Src kinase. Final concentrations of the components of the coupled enzyme system are 2.5 mM phosphoenol-pyruvate, 200 μ M NADH, 30 μ g/ml pyruvate kinase and 10 μ g/ml lactate dehydrogenase.

25 [0181] In a typical assay, all the reaction components with the exception of ATP are pre-mixed and aliquoted into assay plate wells. Inhibitors dissolved in DMSO are added to the wells to give a final DMSO concentration of 2.5%. The assay plate is incubated at 30°C for 10 min 30 before initiating the reaction with 100 μ M ATP. The absorbance change at 340 nm with time, the rate of the reaction, is monitored on a molecular devices plate reader. The data of rate as a function of the inhibitor

concentration is fitted to competitive inhibition kinetics model to get the K_i for the compound.

[0182] Compound IIc-22 was found to have a K_i of less than 0.1 μM for Src.

5

Example 18

[0183] The compounds of this invention can be evaluated as inhibitors of human Lck kinase using either a radioactivity-based assay or spectrophotometric assay.

Lck Inhibition Assay A: Radioactivity-based Assay

10 [0184] The compounds are assayed as inhibitors of full length bovine thymus Lck kinase (from Upstate Biotechnology, cat. no. 14-106) expressed and purified from baculo viral cells. Lck kinase activity is monitored by following the incorporation of ^{33}P from ATP into the tyrosine of a random poly Glu-Tyr polymer substrate of composition, Glu:Tyr = 4:1 (Sigma, cat. no. P-0275). The following are the final concentrations of the assay components: 0.025 M HEPES, pH 7.6, 10 mM MgCl₂, 2 mM DTT, 0.25 mg/ml BSA, 10 μM ATP (1-2 μCi ^{33}P -ATP per reaction), 5 mg/ml poly Glu-Tyr, and 1-2 units of recombinant human Src kinase. In a typical assay, all the reaction components with the exception of ATP are pre-mixed and aliquoted into assay plate wells. Inhibitors dissolved in DMSO are added to the wells to give a final DMSO concentration of 2.5%. The assay plate is incubated at 30°C for 10 min before initiating the reaction with ^{33}P -ATP. After 20 min of reaction, the reactions are quenched with 150 μl of 10% trichloroacetic acid (TCA) containing 20 mM Na₃PO₄. The quenched samples are then transferred to a 96-well filter plate (Whatman, UNI-Filter GF/F Glass Fiber Filter, cat no. 7700-3310) installed on a filter plate vacuum manifold. Filter plates are washed four times with 10% TCA containing 20

mM Na₃PO₄ and then 4 times with methanol. 200µl of scintillation fluid is then added to each well. The plates are sealed and the amount of radioactivity associated with the filters is quantified on a TopCount scintillation counter. The radioactivity incorporated is plotted as a function of the inhibitor concentration. The data is fitted to a competitive inhibition kinetics model to get the K_i for the compound.

Lck Inhibition Assay B: Spectrophotometric Assay

10 [0185] The ADP produced from ATP by the human recombinant Lck kinase-catalyzed phosphorylation of poly Glu-Tyr substrate is quantified using a coupled enzyme assay [Fox et al., Protein Sci., 7:2249(1998)]. In this assay one molecule of NADH is oxidized to NAD for every 15 molecule of ADP produced in the kinase reaction. The disappearance of NADH can be conveniently followed at 340 nm.

20 [0186] The following are the final concentrations of the assay components: 0.025M HEPES, pH 7.6, 10 mM MgCl₂, 2 mM DTT, 5 mg/ml poly Glu-Tyr, and 50 nM of recombinant human Lck kinase. Final concentrations of the components of the coupled enzyme system are 2.5 mM phosphoenol pyruvate, 200 µM NADH, 30 µg/ml pyruvate kinase and 10 µg/ml lactate dehydrogenase.

25 [0187] In a typical assay, all the reaction components with the exception of ATP are pre-mixed and aliquoted into assay plate wells. Inhibitors dissolved in DMSO are added to the wells to give a final DMSO concentration of 2.5%. The assay plate is incubated at 30 °C for 10 min 30 before initiating the reaction with 150 µM ATP. The absorbance change at 340 nm with time, the rate of the reaction, is monitored on a molecular devices plate reader. The data of rate as a function of the inhibitor

concentration is fitted to competitive inhibition kinetics model to get the K_i for the compound.

[0188] Compound IIc-22 was found to have a K_i of less than 0.1 μM for Lck. Compounds IIa-25 and IIa-31 were 5 found to have a K_i between 0.1 and 1.0 μM for Lck.

Example 19

Inhibition of Aurora Assay

[0189] Compounds are screened in the following manner 10 for their ability to inhibit Aurora using a standard coupled enzyme assay (Fox et al (1998) Protein Sci 7, 2249). To an assay stock buffer solution containing 0.1M HEPES 7.5, 10 mM MgCl₂, 1 mM DTT, 25 mM NaCl, 2.5 mM phosphoenolpyruvate, 300 mM NADH, 30 mg/ml pyruvate 15 kinase, 10 mg/ml lactate dehydrogenase, 40 mM ATP, and 800 μM peptide (LRRASLG, American Peptide, Sunnyvale, CA) is added a DMSO solution of a compound of the present invention to a final concentration of 30 μM . The resulting mixture is incubated at 30 °C for 10 minutes. 20 The reaction is initiated by the addition of 10 μL of Aurora stock solution to give a final concentration of 70 nM in the assay. The rates of reaction are obtained by monitoring absorbance at 340 nm over a 5 minute read time at 30 °C using a BioRad Ultramark plate reader (Hercules, 25 CA). The K_i values are determined from the rate data as a function of inhibitor concentration.

[0190] The following compounds were shown to have K_i values less than 0.1 μM for Aurora-2: IIa-24, IIa-25, IIa-26, and IIa-31. The following compounds were shown 30 to have K_i values between 0.1 and 1.0 μM for Aurora-2: IIa-28, IIa-30, IIa-32, and IIc-23. The following compounds were shown to have K_i values greater than 1.0 μM

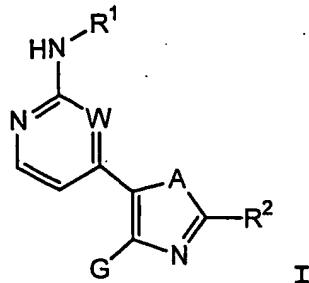
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for Aurora-2: IIc-22, IIc-24, IIc-25, IIc-28, IIc-29,
IIc-30, IIc-31, IIc-32, IIc-33, IIc-34, IIc-35, IIc-36,
IIc-36, IIc-37, IIc-38, IIc-39, and IIc-42.

5 [0191] While we have described a number of embodiments
of this invention, it is apparent that our basic examples
may be altered to provide other embodiments which utilize
the compounds and methods of this invention. Therefore,
it will be appreciated that the scope of this invention
10 is to be defined by the appended claims rather than by
the specific embodiments which have been represented by
way of example.

Claims:

1. A compound of formula I:



or a pharmaceutically acceptable derivative thereof,
wherein:

W is nitrogen or CH;

G is hydrogen or C₁₋₃ aliphatic wherein one methylene unit
of G is optionally replaced by -C(O)-, -C(O)O-,
-C(O)NH-, -SO₂-, or -SO₂NH-;

A is -N-T_(n)-R, oxygen, or sulfur;

R¹ is selected from -T_(n)-R or -T_(n)-Ar¹;

each n is independently 0 or 1;

T is a C₁₋₄ alkylidene chain wherein one methylene unit of
T is optionally replaced by -C(O)-, -C(O)O-, -C(O)NH-,
-SO₂-, or -SO₂NH-;

Ar¹ is a 3-7 membered monocyclic saturated, partially
saturated or aromatic ring having 0-3 heteroatoms
independently selected from nitrogen, oxygen, or
sulfur, or a 8-10 membered bicyclic saturated,
partially saturated or aromatic ring having 0-5
heteroatoms independently selected from nitrogen,
oxygen, or sulfur, wherein each member of Ar¹ is
optionally substituted with one -Z-R³ and one to three
additional groups independently selected from -R,
halogen, oxo, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R,
-NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -OC(O)R,
-C(O)N(R)₂, -OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂,
-NRSO₂R, -NRSO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R;

each R is independently selected from hydrogen or a C₁₋₆ aliphatic, wherein said aliphatic is optionally substituted with one to three groups independently selected from oxo, -CO₂R', -OR', -N(R')₂, -SR', -NO₂, -NR'C(O)R', -NR'C(O)N(R')₂, -NR'CO₂R', -C(O)R', -OC(O)R', -C(O)N(R')₂, -OC(O)N(R')₂, -S(O)R', -SO₂R', -SO₂N(R')₂, -NR'SO₂R', -NR'SO₂N(R')₂, -C(O)C(O)R', -C(O)CH₂C(O)R', halogen, or -CN, or two R bound to the same nitrogen atom are taken together with that nitrogen atom to form a five or six membered heterocyclic or heteroaryl ring having one to two additional heteroatoms independently selected from oxygen, nitrogen, or sulfur;

each R' is independently selected from hydrogen or C₁₋₆ aliphatic, wherein said aliphatic is optionally substituted with one to three groups independently selected from oxo, -CO₂H, -OH, -NH₂, -SH, -NO₂, -NHC(O)H, -NHC(O)NH₂, -NHCO₂H, -C(O)H, -OC(O)H, -C(O)NH₂, -OC(O)NH₂, -S(O)H, -SO₂H, -SO₂NH₂, -NHSO₂H, -NHSO₂NH₂, -C(O)C(O)H, -C(O)CH₂C(O)H, halogen, or -CN, or two R' bound to the same nitrogen atom are taken together with that nitrogen atom to form a five or six membered heterocyclic or heteroaryl ring optionally having one or two additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Z is a C₁-C₆ alkylidene chain wherein up to two non-adjacent methylene units of Z are optionally replaced by -C(O)-, -C(O)O-, -C(O)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)N(R)-, -N(R)N(R)C(O)-, -N(R)C(O)-, -N(R)C(O)O-, -N(R)C(O)N(R)-, -S(O)-, -SO₂- , -N(R)SO₂- , -SO₂N(R)-, -N(R)SO₂N(R)-, -O-, -S-, or -N(R)-;

R² is -Q_(n)-Ar²;

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Ar^2 is selected from a 3-7 membered monocyclic saturated, saturated or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 8-10 membered bicyclic saturated, saturated or aromatic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each member of Ar^2 is optionally substituted with 1-5 groups independently selected from $-\text{Z}-\text{R}^3$, $-\text{R}$, halogen, oxo, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{NRC(O)R}$, $-\text{NRC(O)N}(\text{R})_2$, $-\text{NRCO}_2\text{R}$, $-\text{C(O)R}$, $-\text{CO}_2\text{R}$, $-\text{OC(O)R}$, $-\text{C(O)N}(\text{R})_2$, $-\text{OC(O)N}(\text{R})_2$, $-\text{S(O)R}$, $-\text{SO}_2\text{R}$, $-\text{SO}_2\text{N}(\text{R})_2$, $-\text{N}(\text{R})\text{SO}_2\text{R}$, $-\text{N}(\text{R})\text{SO}_2\text{N}(\text{R})_2$, $-\text{C(O)C(O)R}$, or $-\text{C(O)CH}_2\text{C(O)R}$;

Q is a C_{1-3} alkylidene chain wherein up to two non-adjacent methylene units of Q are optionally replaced by $-\text{C(O)-}$, $-\text{C(O)O-}$, $-\text{C(O)C(O)-}$, $-\text{C(O)N(R)-}$, $-\text{OC(O)N(R)-}$, $-\text{N(R)N(R)-}$, $-\text{N(R)N(R)C(O)-}$, $-\text{N(R)C(O)-}$, $-\text{N(R)C(O)O-}$, $-\text{N(R)C(O)N(R)-}$, $-\text{S(O)-}$, $-\text{SO}_2-$, $-\text{N(R)SO}_2-$, $-\text{SO}_2\text{N(R)-}$, $-\text{N(R)SO}_2\text{N(R)-}$, $-\text{O-}$, $-\text{S-}$, or $-\text{N(R)-}$;

R^3 is selected from $-\text{Ar}^3$, $-\text{R}$, halogen, $-\text{NO}_2$, $-\text{CN}$, $-\text{OR}$, $-\text{SR}$, $-\text{N}(\text{R})_2$, $-\text{NRC(O)R}$, $-\text{NRC(O)N}(\text{R})_2$, $-\text{NRCO}_2\text{R}$, $-\text{C(O)R}$, $-\text{CO}_2\text{R}$, $-\text{OC(O)R}$, $-\text{C(O)N}(\text{R})_2$, $-\text{OC(O)N}(\text{R})_2$, $-\text{SOR}$, $-\text{SO}_2\text{R}$, $-\text{SO}_2\text{N}(\text{R})_2$, $-\text{NRSO}_2\text{R}$, $-\text{NRSO}_2\text{N}(\text{R})_2$, $-\text{C(O)C(O)R}$, or $-\text{C(O)CH}_2\text{C(O)R}$; and

Ar^3 is a 5-6 membered saturated, partially saturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each member of Ar^3 is optionally substituted with halogen, oxo, $-\text{CN}$, $-\text{NO}_2$, $-\text{R}'$, $-\text{OR}'$, $-\text{N}(\text{R}')_2$, $-\text{N}(\text{R}')\text{C(O)R}'$, $-\text{N}(\text{R}')\text{C(O)N}(\text{R}')_2$, $-\text{N}(\text{R}')\text{CO}_2\text{R}'$, $-\text{C(O)R}'$, $-\text{CO}_2\text{R}'$, $-\text{OC(O)R}'$, $-\text{C(O)N}(\text{R}')_2$, $-\text{OC(O)N}(\text{R}')_2$, or $-\text{SO}_2\text{R}'$;

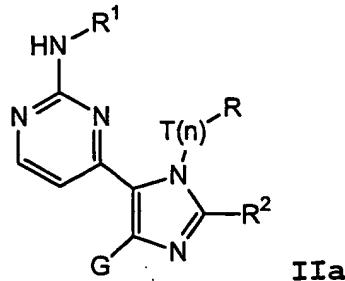
provided that when W is nitrogen and:

(i) A is $-\text{N-T}_{(n)}-\text{R}$ and R^2 is a saturated ring or

- 111 -

(ii) A is sulfur,
then R¹ is other than an optionally substituted phenyl.

2. The compound according to claim 1, wherein said compound has formula IIa:



or a pharmaceutically acceptable derivative thereof.

3. The compound according to claim 2, wherein said compound has one or more features selected from the group consisting of:

(a) R¹ is hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene chain and Ar¹ is a 6-membered saturated, partially saturated, or aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each member of R¹ is optionally substituted with one -Z-R³ and one to three additional groups independently selected from -CO₂R, -OR, halogen, -NRSO₂R, -SO₂N(R)₂, -NRCON(R)₂, -NO₂, or -N(R)₂;

(b) R² is Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar² is optionally substituted with one to five groups independently selected from -Z-R³, -R, halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂,

-OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R,
-N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R; and

(c) G is hydrogen.

4. The compound according to claim 3, wherein said compound has one or more features selected from the group consisting of:

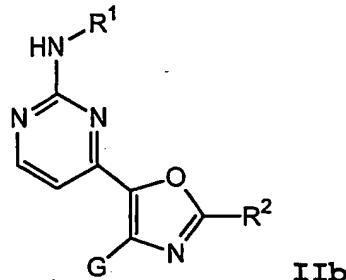
(a) R¹ is selected from a phenyl, benzyl, pyridyl, piperidinyl, or cyclohexyl ring, wherein said ring is optionally substituted with benzyloxy, phenoxy, -SO₂NH₂, -OH, -NO₂, -NH₂, -OMe, -Br, -Cl, -CO₂Me, -NHSO₂Me, -NHSO₂Et, -NHCON(Me)₂, -NHCON(Et)₂, -NHCOpyrrolidin-1-yl, -NHCOMorpholin-4-yl, -O-CH₂-phenyl, -O(CH₂)₃OH, -O(CH₂)₃NH(CH₂)₂OH, -O(CH₂)₂NH(CH₂)₂OH, -O(CH₂)₃N(hydroxyethyl)(methyl), -O(CH₂)₃pyrrolidin-1-yl, -O(CH₂)₂morpholin-4-yl, -O(CH₂)₃N(Me)₂, -O(CH₂)₃N(Et)₂, -O(CH₂)₃(4-hydroxyethyl piperazin-1-yl), -O(CH₂)₃piperazin-1-yl, -O(CH₂)₃(4-hydroxymethylpiperidin-1-yl), -O(CH₂)₃(4-hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂, -NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-aminothiazol-4-yl), -NHCOCH₂cyclopropyl, -NHCO(CH₂)₂N(Et)₂, -NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl, -NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl;

(b) R² is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein R² is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo,

fluoro, trifluoromethyl, -OH, -NH₂, methyl, methoxy, or ethoxy; and

(c) G is hydrogen.

5. The compound according to claim 1, wherein said compound has the formula **IIb**:



or a pharmaceutically acceptable derivative thereof.

6. The compound according to claim 5, wherein said compound has one or more features selected from the group consisting of:

(a) R¹ is hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene chain and Ar¹ is a 6-membered saturated, partially saturated, or aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each member of R¹ is optionally substituted with one -Z-R³ and one to three additional groups independently selected from -CO₂R, -OR, halogen, -NRSO₂R, -SO₂N(R)₂, -NRCON(R)₂, -NO₂, or -N(R)₂;

(b) R² is Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar² is optionally substituted with one to five groups independently selected from -Z-R³, -R, halogen, -NO₂, -CN, -OR, -SR, -N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRCO₂R, -C(O)R, -CO₂R, -C(O)N(R)₂,

-OC(O)N(R)₂, -S(O)R, -SO₂R, -SO₂N(R)₂, -N(R)SO₂R,
-N(R)SO₂N(R)₂, -C(O)C(O)R, or -C(O)CH₂C(O)R; and

(c) G is hydrogen.

7. The compound according to claim 6, wherein said compound has one or more features selected from the group consisting of:

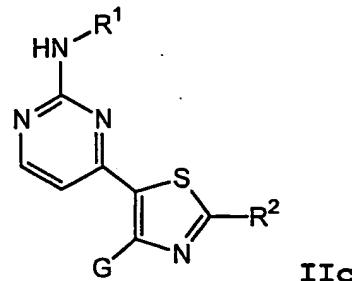
(a) R¹ is selected from a phenyl, benzyl, pyridyl, piperidinyl, or cyclohexyl ring, wherein said ring is optionally substituted with benzyloxy, phenoxy, -SO₂NH₂, -OH, -NO₂, -NH₂, -OMe, -Br, -Cl, -CO₂Me, -NHSO₂Me, -NHSO₂Et, -NHCON(Me)₂, -NHCON(Et)₂, -NHCOpyrrolidin-1-yl, -NHCOMorpholin-4-yl, -O-CH₂-phenyl, -O(CH₂)₃OH, -O(CH₂)₃NH(CH₂)₂OH, -O(CH₂)₂NH(CH₂)₂OH, -O(CH₂)₃N(hydroxyethyl)(methyl), -O(CH₂)₃pyrrolidin-1-yl, -O(CH₂)₂morpholin-4-yl, -O(CH₂)₃N(Me)₂, -O(CH₂)₃N(Et)₂, -O(CH₂)₃(4-hydroxyethyl piperazin-1-yl), -O(CH₂)₃piperazin-1-yl, -O(CH₂)₃(4-hydroxymethylpiperidin-1-yl), -O(CH₂)₃(4-hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂, -NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-aminothiazol-4-yl), -NHCOCH₂cyclopropyl, -NHCO(CH₂)₂N(Et)₂, -NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl, -NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl;

(b) R² is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein R² is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo,

fluoro, trifluoromethyl, -OH, -NH₂, methyl, methoxy, or ethoxy; and

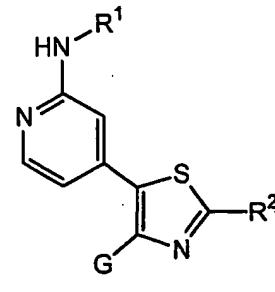
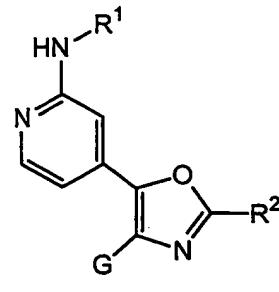
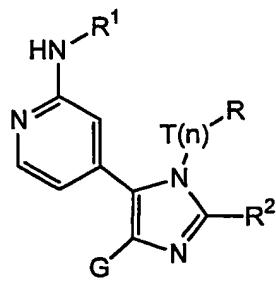
(c) G is hydrogen.

8. The compound according to claim 1, wherein said compound has the formula **IIc**:



or a pharmaceutically acceptable derivative thereof.

9. The compound according to claim 1, wherein said compound has the formula **IIIa**, **IIIb** or **IIIc**:



or a pharmaceutically acceptable derivative thereof.

10. The compound according to claim 8 or 9, wherein said compound has one or more features selected from the group consisting of:

(a) R¹ is hydrogen, Ar¹ or -T-Ar¹ wherein T is a C₁₋₄ alkylidene chain and Ar¹ is a 6-membered saturated, partially saturated, or aryl ring having zero to two heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each member of R¹ is optionally substituted with one -Z-R³ and one to three additional

groups independently selected from $-CO_2R$, $-OR$, halogen, $-NRSO_2R$, $-SO_2N(R)_2$, $-NRCON(R)_2$, $-NO_2$, or $-N(R)_2$;

(b) R^2 is Ar^2 or $-CH_2-Ar^2$ wherein Ar^2 is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar^2 is optionally substituted with one to five groups independently selected from $-Z-R^3$, $-R$, halogen, $-NO_2$, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRCO_2R$, $-C(O)R$, $-CO_2R$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-S(O)R$, $-SO_2R$, $-SO_2N(R)_2$, $-N(R)SO_2R$, $-N(R)SO_2N(R)_2$, $-C(O)C(O)R$, or $-C(O)CH_2C(O)R$; and

(c) G is hydrogen.

11. The compound according to claim 10, wherein said compound has one or more features selected from the group consisting of:

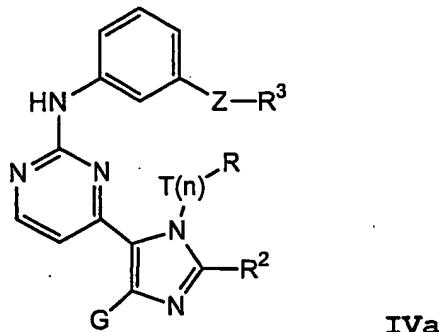
(a) R^1 is selected from a phenyl, benzyl, pyridyl, piperidinyl, or cyclohexyl ring, wherein said ring is optionally substituted with benzyloxy, phenoxy, $-SO_2NH_2$, $-OH$, $-NO_2$, $-NH_2$, $-OMe$, $-Br$, $-Cl$, $-CO_2Me$, $-NHSO_2Me$, $-NHSO_2Et$, $-NHCON(Me)_2$, $-NHCON(Et)_2$, $-NHCOpyrrolidin-1-yl$, $-NHCOMorpholin-4-yl$, $-O-CH_2-phenyl$, $-O(CH_2)_3OH$, $-O(CH_2)_3NH(CH_2)_2OH$, $-O(CH_2)_2NH(CH_2)_2OH$, $-O(CH_2)_3N(\text{hydroxyethyl})(methyl)$, $-O(CH_2)_3\text{pyrrolidin-1-yl}$, $-O(CH_2)_2morpholin-4-yl$, $-O(CH_2)_3N(Me)_2$, $-O(CH_2)_3N(Et)_2$, $-O(CH_2)_3(4\text{-hydroxyethyl piperazin-1-yl})$, $-O(CH_2)_3\text{piperazin-1-yl}$, $-O(CH_2)_3(4\text{-hydroxymethylpiperidin-1-yl})$, $-O(CH_2)_3(4\text{-hydroxypiperidin-1-yl})$, $-NHCO(CH_2)_3N(Me)_2$, $-NHCO(CH_2)_3NCOCH_3$, $-NHCOCH_2\text{pyridin-2-yl}$, $-NHCOCH_2(2\text{-aminothiazol-4-yl})$, $-NHCOCH_2\text{cyclopropyl}$, $-NHCO(CH_2)_2N(Et)_2$, $-NHCO(CH_2)_2-(\text{piperazin-2,5-dione-3-yl})$, $-NHCO_2CH_2\text{tetrahydrofuran-2-yl}$, $-NHCO_2\text{tetrahydrofuran-2-yl}$,

-NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl;

(b) R² is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein R² is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo, fluoro, trifluoromethyl, -OH, -NH₂, methyl, methoxy, or ethoxy; and

(c) G is hydrogen.

12. The compound according to claim 1, wherein said compound has the formula IVa:



or a pharmaceutically acceptable derivative thereof.

13. The compound according to claim 12, wherein said compound has one or more features selected from the group consisting of:

(a) R² is Ar² or -CH₂-Ar² wherein Ar² is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar² is optionally substituted by wherein Ar² is optionally substituted with one to five

groups independently selected from $-Z-R^3$, $-R$, halogen, $-NO_2$, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRCO_2R$, $-C(O)R$, $-CO_2R$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-S(O)R$, $-SO_2R$, $-SO_2N(R)_2$, $-N(R)SO_2R$, $-N(R)SO_2N(R)_2$, $-C(O)C(O)R$, or $-C(O)CH_2C(O)R$;

(b) G is hydrogen;

(c) Z is a C_{1-4} alkylidene chain wherein one methylene unit of Z is optionally replaced by $-O-$, $-NH-$, $-NHC(O)-$, $-NHC(O)O-$, $-NHSO_2-$, $-C(O)NH-$; and

(d) R^3 is selected from $-N(R)_2$, $-NHC(O)R$, or Ar^3 wherein Ar^3 is a 5-6 membered heterocyclic or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen, or sulfur and Ar^3 is optionally substituted with $-R'$, $-OR'$, $-N(R')_2$, or oxo.

14. The compound according to claim 13, wherein said compound has one or more features selected from the group consisting of:

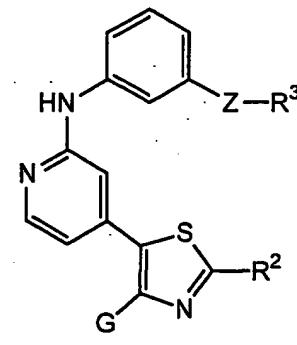
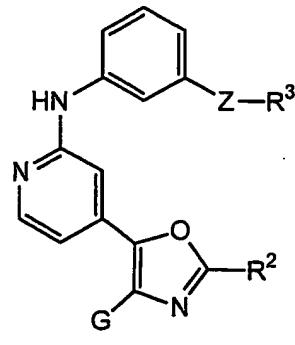
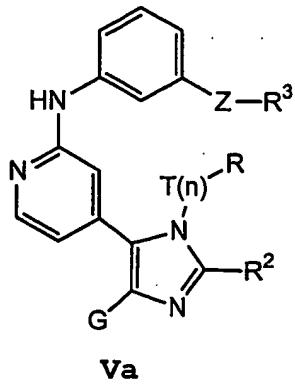
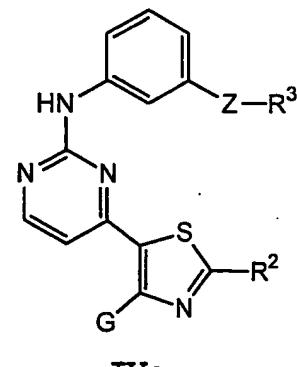
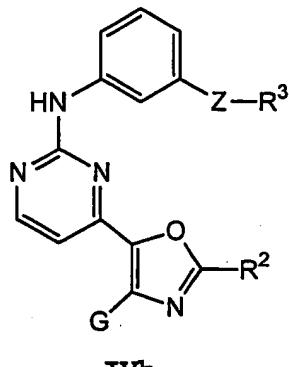
(a) R^2 is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein each member of R^2 is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl, pyrimidinyl, chloro, bromo, fluoro, trifluoromethyl, $-OH$, $-NH_2$, methyl, methoxy, or ethoxy;

(b) G is hydrogen; and

(c) $-Z-R^3$ is selected from $-O-CH_2-phenyl$, $-O(CH_2)_3OH$, $-O(CH_2)_3NH(CH_2)_2OH$, $-O(CH_2)_2NH(CH_2)_2OH$, $-O(CH_2)_3N(hydroxyethyl)(methyl)$, $-O(CH_2)_3pyrrolidin-1-yl$, $-O(CH_2)_2morpholin-4-yl$, $-O(CH_2)_3N(Me)_2$, $-O(CH_2)_3N(Et)_2$,

-O(CH₂)₃(4-hydroxyethyl piperazin-1-yl), -O(CH₂)₃piperazin-1-yl, -O(CH₂)₃(4-hydroxymethylpiperidin-1-yl), -O(CH₂)₃(4-hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂, -NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-aminothiazol-4-yl), -NHCOCH₂cyclopropyl, -NHCO(CH₂)₂N(Et)₂, -NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHC(O)-pyrrolidin-1-yl, -NHCOmorpholin-4-yl, -NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl, -NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl.

15. The compound according to claim 1, wherein said compound has the formula IVb, IVc, Va, Vb, or Vc:



or a pharmaceutically acceptable derivative thereof.

16. The compound according to claim 15, wherein said compound has one or more features selected from the group consisting of:

(a) R^2 is Ar^2 or $-CH_2-Ar^2$ wherein Ar^2 is selected from 5-6 membered ring selected from carbocyclic, aryl, or a heterocyclyl or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen or sulfur, and wherein Ar^2 is optionally substituted by wherein Ar^2 is optionally substituted with one to five groups independently selected from $-Z-R^3$, $-R$, halogen, $-NO_2$, $-CN$, $-OR$, $-SR$, $-N(R)_2$, $-NRC(O)R$, $-NRC(O)N(R)_2$, $-NRCO_2R$, $-C(O)R$, $-CO_2R$, $-C(O)N(R)_2$, $-OC(O)N(R)_2$, $-S(O)R$, $-SO_2R$, $-SO_2N(R)_2$, $-N(R)SO_2R$, $-N(R)SO_2N(R)_2$, $-C(O)C(O)R$, or $-C(O)CH_2C(O)R$;

(b) G is hydrogen;

(c) Z is a C_{1-4} alkylidene chain wherein one methylene unit of Z is optionally replaced by $-O-$, $-NH-$, $-NHC(O)-$, $-NHC(O)O-$, $-NHSO_2-$, $-C(O)NH-$; and

(d) R^3 is selected from $-N(R)_2$, $-NHC(O)R$, or Ar^3 wherein Ar^3 is a 5-6 membered heterocyclic or heteroaryl ring having one to two heteroatoms independently selected from nitrogen, oxygen, or sulfur and Ar^3 is optionally substituted with $-R'$, $-OR'$, $-N(R')_2$, or oxo.

17. The compound according to claim 16, wherein said compound has one or more features selected from the group consisting of:

(a) R^2 is selected from phenyl, pyridyl, pyrimidinyl, cyclohexyl, piperidinyl, furanyl, or benzyl, wherein each member of R^2 is optionally substituted with phenyl, phenoxy, benzyl, benzyloxy, pyridyl, 3-hydroxyphenyl, 2-hydroxyphenyl, 3-aminophenyl, N-BOC-pyrrolyl, 4-chlorophenyl, 3-ethoxypyridyl, 2-methoxypyridyl, 2,5-dimethylisoxazolyl, 3-ethoxyphenyl, 4-isopropylphenyl, 4-F-3-Cl-phenyl, pyrrolyl,

pyrimidinyl, chloro, bromo, fluoro, trifluoromethyl, -OH, -NH₂, methyl, methoxy, or ethoxy;

(b) G is hydrogen; and

(c) -Z-R³ is selected from -O-CH₂-phenyl, -O(CH₂)₃OH, -O(CH₂)₃NH(CH₂)₂OH, -O(CH₂)₂NH(CH₂)₂OH, -O(CH₂)₃N(hydroxyethyl)(methyl), -O(CH₂)₃pyrrolidin-1-yl, -O(CH₂)₂morpholin-4-yl, -O(CH₂)₃N(Me)₂, -O(CH₂)₃N(Et)₂, -O(CH₂)₃(4-hydroxyethyl piperazin-1-yl), -O(CH₂)₃piperazin-1-yl, -O(CH₂)₃(4-hydroxymethylpiperidin-1-yl), -O(CH₂)₃(4-hydroxypiperidin-1-yl), -NHCO(CH₂)₃N(Me)₂, -NHCO(CH₂)₃NCOCH₃, -NHCOCH₂pyridin-2-yl, -NHCOCH₂(2-aminothiazol-4-yl), -NHCOCH₂cyclopropyl, -NHCO(CH₂)₂N(Et)₂, -NHCO(CH₂)₂-(piperazin-2,5-dione-3-yl), -NHC(O)-pyrrolidin-1-yl, -NHCOMorpholin-4-yl, -NHCO₂CH₂tetrahydrofuran-2-yl, -NHCO₂tetrahydrofuran-2-yl, -NHCO₂tetrahydropyran-4-yl, or -NHCO₂CH₂tetrahydropyran-2-yl.

18. The compound according to claim 1 selected from those listed in Tables 1-5.

19. A composition comprising a compound according to any one of claims 1 to 18, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

20. The composition according to claim 19, additionally comprising a therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes,

an agent for treating immunodeficiency disorders, or an agent for treating cancer.

21. A method of inhibiting JNK, Lck, Src, or Aurora-2 kinase activity in a biological sample comprising the step of contacting said biological sample with:

- (a) a compound according to claim 1; or
- (b) a composition according to claim 19.

22. A method of treating or lessening the severity of a JNK-, Lck-, Src-, or Aurora-2-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to claim 19.

23. A method of treating or lessening the severity of an inflammatory disease, autoimmune disease, destructive bone disorder, proliferative disorder, infectious disease, neurodegenerative disease, allergy, reperfusion/ischemia in stroke, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation, or a condition associated with proinflammatory cytokines, comprising the step of administering to said patient a composition according to claim 19.

24. The method according to claim 23, wherein said method is used to treat or prevent an inflammatory disease selected from acute pancreatitis, chronic pancreatitis, asthma, allergies, or adult respiratory distress syndrome.

25. The method according to claim 23, wherein said method is used to treat or prevent an autoimmune

disease selected from glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

26. The method according to claim 23, wherein said method is used to treat or prevent a destructive bone disorders selected from osteoarthritis, osteoporosis or multiple myeloma-related bone disorder.

27. The method according to claim 23, wherein said method is used to treat or prevent a proliferative disease selected from acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, .

28. The method according to claim 23, wherein said method is used to treat or prevent neurodegenerative disease selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, cerebral ischemia or neurodegenerative disease caused by traumatic injury, glutamate neurotoxicity or hypoxia.

29. The method according to claim 23, wherein said method is used to treat or prevent ischemia/reperfusion in stroke or myocardial ischemia, renal ischemia, heart attacks, organ hypoxia or thrombin-induced platelet aggregation.

30. The method according to claim 23, wherein said method is used to treat or prevent a condition associated with T-cell activation or pathologic immune responses.

31. The method according to claim 23, wherein said method is used to treat or prevent an angiogenic disorder selected from solid tumors, ocular neovasculization, or infantile haemangiomas.

32. The method according to claim 22, wherein said disease is selected from hypercalcemia, restenosis, hypercalcemia, osteoporosis, osteoarthritis, symptomatic treatment of bone metastasis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, Hashimoto's thyroiditis, Guillain-Barre syndrome, chronic obstructive pulmonary disorder, contact dermatitis, cancer, Paget's disease, asthma, ischemic or reperfusion injury, allergic disease, atopic dermatitis, or allergic rhinitis.

33. The method according to claim 32, wherein said disease is selected from hypercalcemia, osteoporosis, osteoarthritis, or symptomatic treatment of bone metastasis.

34. The method according to claim 22, wherein said disease is selected from autoimmune diseases, allergies, rheumatoid arthritis, or leukemia.

35. The method according to claim 22, wherein said disease is selected from melanoma, leukemia, or a cancer selected from colon, breast, gastric, ovarian,

cervical, melanoma, renal, prostate, lymphoma, neuroblastoma, pancreatic, leukemia and bladder.

36. The method according to claim 22, comprising the additional step of administering to said patient an additional therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and

said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

37. A composition for coating an implantable device comprising a compound according to claim 1 and a carrier suitable for coating said implantable device.

38. An implantable device coated with a composition according to claim 37.

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D403/04	A61K31/505	A61P29/00	C07D413/04	C07D417/04
	C07D401/14	C07D417/14	C07D403/14	C07D413/14	C07D401/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *&* document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 November 2003	26/11/2003
Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel: (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Steendijk, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LIPINSKI C A ET AL: "BIOISOSTERIC PROTOTYPE DESIGN OF BIARYL IMIDAZOLYL AND TRIAZOLYL COMPETITIVE HISTAMINE H-2-RECEPTOR ANTAGONISTS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 29, no. 11, 1986, pages 2154-2163, XP002260193 ISSN: 0022-2623 see page 2161, precursors in scheme IV	1,9, 15-17
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